THE SURGICAL CLINICS OF NORTH AMERICA

APRIL 1975

SURGERY OF THE LIVER, SPLEEN AND PANCREAS

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SYMPOSIUM ON
SURGERY OF THE LIVER, SPLEEN, AND PANCREAS

Larry C. Carey, M.D., *Guest Editor*

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Foreword

For the practicing general surgeon the diseases which afflict the liver, pancreas, and spleen provide continuing challenges. There is little which is static concerning these organs, and as old difficulties are met, new ones arise. Now, perhaps as never before, the surgeon must strive to be an internist with special therapeutic skills. For this reason, several of the articles address diagnostic and pathophysiologic considerations. There is no intention to denigrate the importance of technical skill, but rather a desire to emphasize that the possession of technical skill alone is not enough to allow one to be called a surgeon.

In keeping with the general precepts of the *Surgical Clinics of North America*, the material is designed for the student of medicine irrespective of his age or level of training. There is no attempt to be encyclopedic in scope but rather to provide useful information in specific areas for those caring for patients afflicted with certain diseases of the liver, pancreas, and spleen. The information is largely from the personal experience of a group of physicians who deal with these diseases on a regular basis.

The members of the faculty of medicine of The University of Pittsburgh have been most co-operative in their willingness to complete this volume. It is with great pride that I have been able to count myself as their colleague.

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Pathology of the Spleen in Hematologic Disease

Volker Breitfeld, M.D., and Robert E. Lee, M.D.***

The spleen has long been and remains a somewhat mysterious organ of the body. The various functions of the spleen and their morphologic correlates are at present only incompletely understood. Often results of hematologic tests must be known before the surgical pathologist can render a specific diagnosis on a spleen. Ackerman and Rosai aptly point out in the fifth edition of *Surgical Pathology* that there are relatively few significant changes in many diseased spleens and that even these are frequently not diagnostic.[1]

In this article we will compare our experience of the significant gross and microscopic changes of the spleen in various hematologic diseases with that available in the literature.

THE SPLEEN IN HEMATOLOGIC DISEASES

Hereditary Spherocytosis

PATHOGENESIS. Hereditary spherocytosis, the most common of the congenital hemolytic anemias of Caucasian people, shows an autosomal dominant pattern of inheritance. In hereditary spherocytosis, premature destruction of intrinsically abnormal red cells occurs in the presence of the spleen. Despite intensive research, the exact biochemical defect of the red cell membrane remains unknown.[48] Both the genetic red cell membrane abnormality and the exacting microcirculation of the spleen are needed to produce hemolysis. The surgical removal of the spleen renders red cell survival normal and complete remission ensues even though the intrinsic defect of the red cell persists.[48]

Because of a membrane defect, the hereditary spherocytosis cell is abnormally permeable to sodium ions, and secondarily water. Large

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amounts of energy must be expended to maintain a normal equilibrium, by actively pumping sodium out of the cell. In conditions of stagnation, as in the spleen (or the test tube) in which there is a low glucose concentration, the hereditary spherocytosis cell can no longer generate the energy to pump sodium ion out of the cell. Consequently the cell swells, becomes even less plastic and begins to loose surface membrane material. On repeated passages through the spleen, the red blood cell becomes a rigid microspherocyte so classic of hereditary spherocytosis. This microspherocyte is no longer able to deform sufficiently to get through the fenestrated basement membrane of the splenic sinus, and is destroyed in the splenic cords.[18] Jandl et al.[52] established that the cells of hereditary spherocytosis show less plasticity than the normal red cells, as evidenced by their inability to transverse tiny Millipore filter openings easily transversed by normal red cells. This decreased plasticity is worsened by an acidic milieu, which exists in the splenic pulp.[75] It can be seen that the spleen, with its exacting and unique microcirculation, plays the crucial role in hereditary spherocytosis.

Both lipid and protein constituents of the red cell membrane have been extensively studied in hereditary spherocytosis. Minor variations in the content and kinetics of lipids of the hereditary spherocytosis red cell membrane have been shown, but may be due to other defects in the membrane.[17] Recently Jacob presented support for the possibility that hereditary spherocytosis represents a mutation in the microfilamentous proteins of the red cell membrane on which the normal biconcave discoid shape of the red blood cell appears to depend.[50] It may be that the variability of severity of hereditary spherocytosis in different families depends on the type of mutation of these contractile microfilament proteins.

PATHOLOGY OF THE SPLEEN. The spleen in hereditary spherocytosis is invariably moderately enlarged to 3 to 6 times its normal weight. Older patients tend to have the largest spleens. In our experience the heaviest spleen weighed 1010 gm (from a 42 year old patient). The average weight of our 18 spleens in adults with hereditary spherocytosis was 640 gm. Rappaport recorded an average weight of 870 gm (range 430 to 1410 gm).[81] Schybergson, as quoted by Wiland, reported a weight of 3500 gm.[104] The splenic capsule is usually smooth and shiny. On cut section, there is intense congestion, the trabeculae are widely separated, and the white pulp is frequently obscure. Three of our cases showed infarcts.

Microscopically, there is intense congestion of the widened splenic cords while the sinuses are usually compressed by the remarkably broadened cords (Fig. 1). The sinuses generally show prominent lining cells. There appears to be an increase of cordal macrophages, but this increase is often obscured by the pronounced red cell stasis in the cords. Erythrophagocytosis is only rarely observed. Hemosiderin pigment is usually increased in cordal macrophages and in sinusoidal endothelial cells. The white pulp is inconspicuous, although Wiland stated that overall it is not decreased but only widely separated by the red pulp.[104] Extramedullary hematopoiesis was invariably found by some ob-

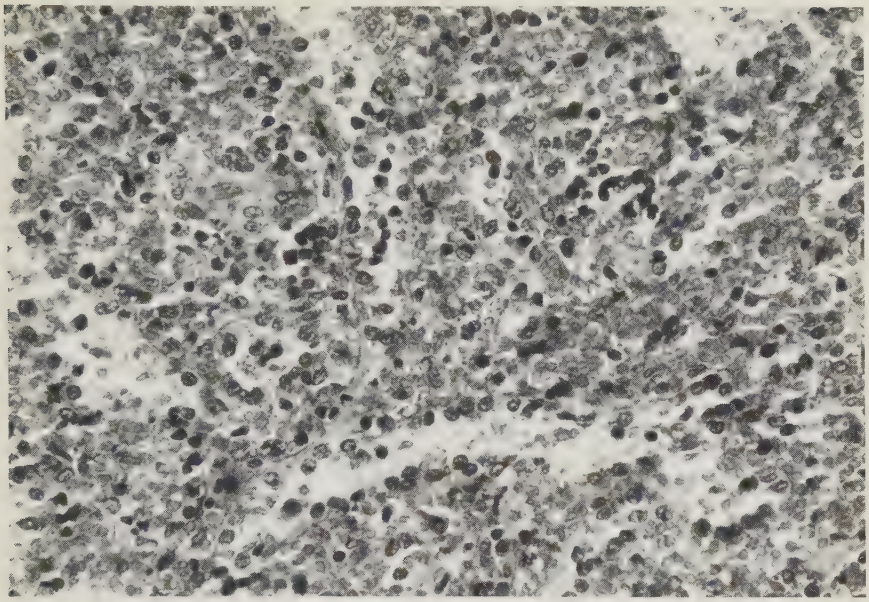

Figure 1. The spleen of congenital spherocytosis. Note the widened splenic cords and the compressed sinuses with prominent lining cells. Hematoxylin-eosin; ×470.

servers,[104] but we have noted it only infrequently. Although by light microscopy the sinuses appear empty, a recent study of the spleen in hereditary spherocytosis at an electron microscopy level showed numerous red cell ghosts in the dilated "empty" splenic sinuses. In addition, breakdown products of hemoglobin were seen both in cordal macrophages and sinus cells.[71]

Autoimmune Hemolytic Anemias

PATHOGENESIS. Acquired autoimmune hemolytic anemias may be either primary (idiopathic) or secondary to a large variety of conditions, principally lymphoreticular malignancies or autoimmune diseases.[25, 26, 94] These hemolytic disorders are characterized by (1) shortened red cell survival, (2) evidence of "autoimmunity" against own cells as manifested by the direct or indirect Coombs' test, and (3) usually erythroid hyperplasia of the marrow.

Fragmentation of red cells after damage by autoantibodies and/or complement appears to be the underlying mechanism of red cell destruction.[97] Damaged red cells tend to become rigid spherocytes that are no longer able to negotiate the splenic microcirculation. The phagocytic cells of the reticuloendothelial system appear to have special receptor sites which interact with red cells coated with antibodies and/or complement.[41, 65] Subsequent erythrophagocytosis of fragments or whole cells ensues principally in the spleen. Erythrophagocytosis in the spleen is commonly found in patients with autoimmune hemolytic anemias.[81]

SPLENIC PATHOLOGY. In idiopathic autoimmune hemolytic anemias the spleen is moderately enlarged, but seldom to the degree seen in spherocytosis. The average weight in our 17 cases was 330 gm (range 170 to 860 gm). The average weight of the spleen in Rappaport's series was 650 gm (range 148 to 1670).[81] The capsule is smooth and unremarkable but may be thickened focally. Generally the cut surface is congested, may be of normal consistency, but at times is firmer or softer than usual. We rarely observed gross infarcts, while Rappaport noted them in 26 per cent of his cases.[81]

Microscopically, the architecture is generally preserved. There is usually marked congestion of the pulp with widened empty or congested sinusoids, and prominent sinusoidal lining cell hyperplasia. The increased amount of red pulp results in more widely separated white pulp which often shows hyperplasia with many active germinal centers. We observed extramedullary hematopoiesis in red pulp areas in only 3 of 17 cases, while Rappaport noted it in about 33 per cent of cases.[81] Hemosiderin pigment may be very prominent in cordal macrophages, less so in sinus lining cells. Erythrophagocytosis was occasionally noted, but in no case was prominent. Rappaport observed it in 80 per cent of his cases, occurring both in cords and sinuses.[81] In Rappaport's series, there was good correlation of red pulp cord congestion and empty sinusoids with the degree of osmotic fragility and spherocytosis of red blood cells; the more spherocytosis, the more marked was the cordal congestion and emptiness of sinusoids.[81]

It is readily appreciated that pathologically the spleen of autoimmune hemolytic anemias may be rather similar to that of hereditary spherocytosis, and without pertinent clinical data the pathologist will have difficulty distinguishing the two entities. It is perhaps possible that the smaller size of the spleen in autoimmune hemolytic anemias simply reflects less splenic work hypertrophy because of shorter duration of disease.

Hereditary Elliptocytosis

PATHOGENESIS. In hereditary elliptocytosis (ovalocytosis), a relatively rare red cell membrane defect, upward of 25 per cent of red cells, and usually more than 50 per cent, have an elliptical shape. The majority of patients show little hemolysis, but in 12 to 15 per cent of patients there is a brisk hemolytic anemia with significantly shortened red cell survival.[24, 60] Hereditary elliptocytosis is inherited in an autosomal dominant fashion, that in some cases appears to be linked to the Rh locus.[24, 73] In cases without Rh linkage, hemolysis is usually more severe.[24, 73] Like the spherocyte of hereditary spherocytosis, the elliptocyte shows increased osmotic fragility and increased permeability to sodium ions.[24] As in hereditary spherocytosis, the spleen is the site of sequestration and destruction of the elliptocyte, and the beneficial effect of splenectomy in those patients with elliptocytosis and marked hemolysis is well documented, although the ovalocytosis persists.[9, 24, 64] It has been postulated that the defect in ovalocytosis resides within the red cell membrane proteins.[35]

SPLEEN PATHOLOGY. In patients with marked hemolysis, the spleen has been invariably moderately enlarged. We have no experience with spleens from such patients. Cutting reported weights from 180 gm in a 4 year old patient to 500 gm in an adult.[24] The gross appearance of the spleen is similar to that seen in spherocytosis.[9, 24]

Microscopically, there is intense cordal congestion and sinusoids appear generally empty and are lined by prominent endothelial cells.[11, 60] Blackburn noted erythrophagocytosis, not commented upon by others.[9] Lipton described, in addition, congested sinusoids in a single case.[64] Wilson et al. described only fibrosis and hemosiderosis.[106]

Thalassemia

PATHOGENESIS. Thalassemia as a term covers a rather heterogeneous group of hereditary disorders, all of which have in common an unbalanced rate of synthesis of one or more of the normal hemoglobin polypeptide chains. Thus thalassemia is perhaps best classified on the basis of the polypeptide chain or chains involved. The scope of these disorders is so vast and complicated that even a short review of this subject is impossible here. Suffice it to say that commonly the peripheral blood shows microcytosis, hypochromia, and marked anisopoikilocytosis of red cells (often treated as iron deficiency by the unsuspecting physician). Generally, the heterozygote (one abnormal gene) is mildly affected (thalassemia minor), whereas the individual with two abnormal identical or similar genes is severely affected by marked anemia, reticulocytosis and splenomegaly (thalassemia major). When thalassemia major is complicated by hypersplenism, splenectomy may be indicated.[12, 23]

SPLEEN PATHOLOGY. The average size of the spleen in patients with thalassemia major is from 3 to 7 times normal.[74] The capsule is generally normal or only slightly thickened, and on cut section there is intense congestion. The white pulp is inconspicuous.

The trabeculae are prominent while the white pulp is frequently atrophic. The most marked changes appear in the red pulp. The sinuses may be congested and dilated. There is marked reticuloendothelial cell hyperplasia, in both cords and sinuses. Extramedullary hematopoiesis is frequently present in the red pulp.[11] Sen Gupta described numerous pale foamy, strongly PAS-positive histiocytes in the red pulp in 4 of 30 cases of thalassemia.[88] In alpha thalassemia (hemoglobin H disease), electron microscopy disclosed two splenic actions upon the abnormal red cells. Intracellular precipitates of beta-chains are removed (pitted) from erythrocytes in the cords as cells with such precipitates attempt to move from cords into sinuses. In addition, larger cells were split into two smaller sphered fragments while traversing into sinuses. Some small RBC fragments were phagocytosed.[102] The above descriptions provide an insight into splenic mechanism of red cell deformation and destruction in thalassemia.

Hemoglobin C (C-C) Disease

PATHOGENESIS. Homozygous hemoglobin C disease, a hereditary hemoglobinopathy with generally mild clinical symptoms, is character-

ized by a moderate hemolytic anemia and splenomegaly. It occurs predominantly in Negroes. In hemoglobin C, glutamic acid in the 6 position of the beta-chains is replaced by lysine, resulting in relative insolubility of the hemoglobin because of electrostatic interaction of the positively charged 6^{lys} areas with negatively charged adjacent alpha-chain areas.[20, 45] This increased intermolecular attraction results in hemoglobin crystallization, increased rigidity, and decreased plasticity of the HbC red cells.[55] The pitting of these crystals by the spleen results in production of rigid microspherocytes and fragments, which are subsequently destroyed in the exacting splenic microcirculation.[29, 55]

SPLEEN PATHOLOGY. The spleens are invariably enlarged. In our one case, the spleen of a 36 year old Negro woman weighed 390 gm. Diggs[29] reported a spleen weighing 2300 gm, and Wheby[103] reported one weighing 1000 gm. The capsule is unremarkable and the cut surface is dark red, firm, and rather homogenous, with obscured white pulp.

Microscopically, there is congestion and widening of the splenic cords. The pulp sinuses are dilated and show rather prominent lining cells. Macrophages containing hemosiderin are numerous in the cords. The white pulp is rather atrophic and widely separated by red pulp.

Idiopathic Thrombocytopenic Purpura

PATHOGENESIS. Idiopathic thrombocytopenic purpura is a diagnosis that is reached by first excluding other causes of thrombocytopenia. Idiopathic thrombocytopenic purpura comprises at least two different varieties—acute and chronic.[6] Acute idiopathic thrombocytopenic purpura occurs predominantly during childhood, while the chronic form is predominantly a disease of adults with a notable female preponderance. The acute form is usually brief and self-limited, consequently requiring little therapy. Splenectomy is generally reserved for chronic idiopathic thrombocytopenic purpura, where it may be of great value.[23]

The classic and heroic experiments of Harrington et al.,[39] in 1951 first demonstrated a plasma factor resulting in thrombocytopenia. Specific platelet antibodies can now be demonstrated in the majority of patients with idiopathic thrombocytopenic purpura.[57, 58] These platelet antibodies appear to be IgG immunoglobulins.[58, 89] The platelet survival in idiopathic thrombocytopenic purpura is markedly shortened,[6] and the spleen is the graveyard of the antibody-coated and damaged platelets.[5, 89] Platelets heavily coated by antibody are also removed in other reticuloendothelial tissue, predominantly the liver.[5, 89] Recently it has been shown that the spleen actually plays a dual role in idiopathic thrombocytopenic purpura. It not only is the filter that removes the damaged platelets but it also appears to be an important site of platelet antibody production.[69]

SPLEEN PATHOLOGY. In idiopathic thrombocytopenic purpura the spleen may be normal or slightly to moderately increased in weight. In our experience, the average weight of 43 spleens was 170 gm, with a range of 77 to 370 gm. Only 6 spleens weighed more than 250 gm. Bowmann found a slightly increased weight of 195 gm.[13] The capsule is usually unremarkable. The cut surface shows a well maintained gross

architecture. The white pulp frequently is rather prominent, although occasionally it is inconspicuous.

The most conspicuous finding on microscopic examination is an increase of secondary follicles with large and active germinal centers (Fig. 2). This finding has been present in most but not all of our cases. These secondary follicles are frequently surrounded by a marginal zone giving rise to a triple layer appearance of the follicle. Most authors have noted similar white pulp changes.[13, 76, 95] The red pulp may show sinusoidal dilatation and/or congestion, and contains the usual number of polymorphonuclear leukocytes, rare eosinophils, and occasional megakaryocytes which in our experience are not numerous. Bowmann et al., however, noted a nonspecific increase in megakaryocytes in the red pulp.[13] Foamy histiocytes can occasionally be detected singly or in groups in the red pulp. The cytoplasm of these contains PAS-positive and Oil-Red-O positive material. Saltzstein described these histiocytes and their histochemical staining characteristics in 6 of 7 spleens removed for idiopathic thrombocytopenic purpura. He speculated that the phospholipid in these histiocytes may be of platelet origin.[84] We have not recognized platelet phagocytosis in the spleen in idiopathic thrombocytopenic purpura. At an ultrastructural level, however, such histiocytes have been shown to contain platelets at various stages of breakdown.[33] Breckenridge et al.[15] claimed that there is a peculiar combination of findings in the spleens of patients with idiopathic thrombocytopenic purpura and lupus erythematosus,[15] but we have noted only prominent "onion-skin" changes of splenic arterioles in lupus patients.

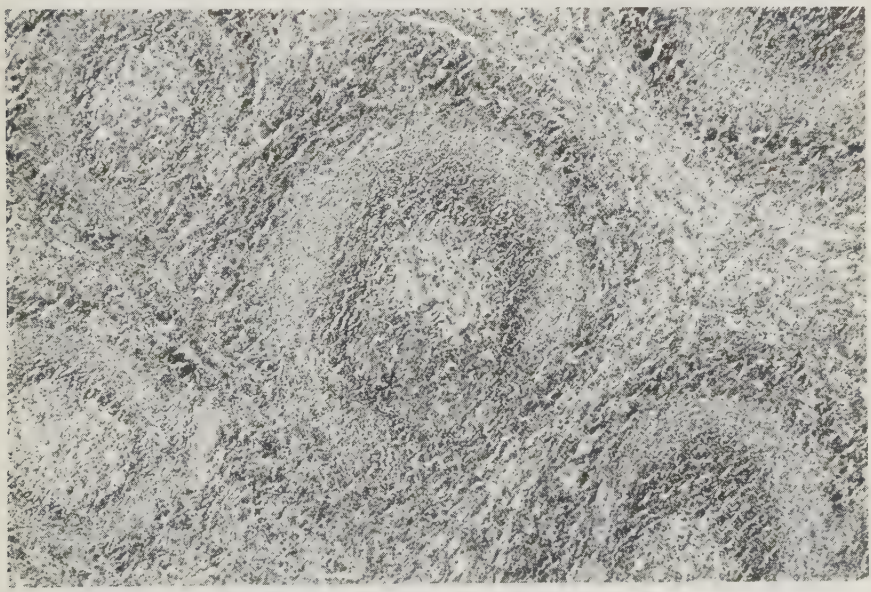

Figure 2. Prominent lymphoid follicles with active germinal centers from a case of idiopathic thrombocytopenic purpura. Hematoxylin-eosin; × 90.

Thrombotic Thrombocytopenic Purpura

PATHOGENESIS. The hallmarks of thrombotic thrombocytopenic purpura are hemolytic anemia with a microangiopathic peripheral blood smear, marked thrombocytopenia, and bizzare and often fluctuating neurologic signs and symptoms. The pathogenesis of this disease remains obscure. The suggestion has been made that thrombotic thrombocytopenic purpura should be thought of as a syndrome that may appear in the course of diseases which affect the microcirculation.[93] The principal histologic alteration in thrombotic thrombocytopenic purpura is the widespread deposition of hyaline acidophilic material within the lumina and beneath the endothelium of arterioles and capillaries.[3, 36] Endothelial proliferation is frequently seen in these areas, but there is conspicuous absence of vasculitis. Immunohistochemical methods and electron microscopy have shown that these intravascular deposits contain principally fibrin and some formed elements of blood.[32] In the recent literature, there have been reports of successful treatment of thrombotic thrombocytopenic purpura with steroids and splenectomy.[42]

SPLEEN PATHOLOGY. In our experience the spleen weighed between 100 and 175 gm in three cases, while it weighed 250 gm in a fourth case. In another case in which thrombotic thrombocytopenic purpura complicated systemic lupus erythematosus, the spleen weighed 500 gm. Grossly and on cut section, the spleens were unremarkable. In other series the spleen was of normal size or slightly to moderately enlarged,[42] and Meacham et al.[70] reported a 500 gm spleen with multiple infarcts.[70]

On microscopic examination, typical intramural and subendothelial hyaline deposits were noted in the arterioles of the periarterial lymphatic sheath and lymphoid follicles of the spleen in our 5 cases. There was no evidence of vasculitis. Microaneurysm at arteriolar-capillary junctions, as reported by Orbison, were not seen, but could have been obscured by cellularity of the white and red pulp. There were no other significant microscopic changes.

Myelofibrosis with Myeloid Metaplasia

PATHOGENESIS. Myelofibrosis with myeloid metaplasia is a well established clinical and pathologic entity in the spectrum of the myeloproliferative syndromes. Its distinctive clinical course and laboratory data usually permit a separation from other entities in that spectrum. Myelofibrosis with myeloid metaplasia affects primarily middle-aged and older people, and its prolonged natural course includes progressive and massive splenomegaly, frequently complicated by hypersplenism affecting red cells and platelets.[11, 37, 90, 92, 96] Hickling[41] and later Jackson et al.[46] did call attention to the high mortality following splenectomies in myelofibrosis with myeloid metaplasia, and subsequently the belief arose that splenectomy had a disastrous effect because the most important organ of blood formation was removed. Green et al.,[37] however, pointed out beneficial effects of splenectomies and argued that much of the mortality reported to occur after splenectomies was due to postoperative complications. The value of splenectomies, especially in those cases

complicated by secondary hypersplenism, is now no longer in doubt,[11, 37, 96] and it is generally believed that the myeloid metaplasia, rather than being compensatory to marrow failure, is part of a general myeloproliferative process.

SPLEEN PATHOLOGY. The spleen is often massively enlarged in myelofibrosis with myeloid metaplasia. Our three splenectomy specimens only ranged from 720 to 1150 gm. In Bournocle's series, the largest spleen weighed 8750 gm, most weighed between 1000 gm and 4000 gm, while only a few weighed less than 350 gm.[11] The capsule may be focally thickened from underlying infarcts, as in one of our cases. On cut section, the spleen is firm, dark brown with inconspicuous and widely separated white pulp. Infarcts are not uncommon. Distinct nodules of varying size, representing extramedullary hematopoiesis may be noted.[1, 80]

Microscopically, the basic splenic architecture is preserved, although the white pulp is often atrophic and compressed. The red pulp shows extensive extramedullary hematopoiesis—both in sinusoids and cords. Extramedullary hematopoiesis is not seen in the white pulp.[96] The extramedullary hematopoiesis involves the trilineage of myeloid cells—that is, immature and mature meyloid, and erythroid and megakaryocytic precursors, none proliferating to the exclusion of the others. Erythroid proliferation is often in distinct foci,[92] just as it is normally seen in the marrow. The cordal and sinusoidal macrophages, often containing hemosiderin, are markedly increased in number and there is variable, though frequently marked red pulp fibrosis.[11, 80, 92, 96] At an ultrastructural level, there is evidence of extensive phagocytosis of maturing myeloid precursors by splenic macrophages. Nuclear and cytoplasmic abnormalities of the hemopoietic precursors are frequently noted.[92]

Leukemic Reticuloendotheliosis

PATHOGENESIS. Recently there have been numerous reports of a rarely recognized neoplastic disease of lymphoreticular cells called leukemic reticuloendotheliosis or "hairy cell" leukemia. Clinically this disease affects predominantly males, has an insidious onset and chronic course, presenting with often massive splenomegaly, little lymphadenopathy and pancytopenia.[18, 59, 86, 108] Characteristic "hairy cells," so called because of numerous cytoplasmic filamentous projections, are seen by phase microscopy in peripheral blood, bone marrow, and tissues such as spleen.[59, 86, 87] These hairy cells, which may be rare in peripheral blood, contain a cytoplasmic tartrate-resistant isoenzyme of acid phosphatase.[107, 108] Whether this hairy cell is of lymphoid or monocyte origin has as yet not been definitely established. Splenectomy has been advocated as the therapy of choice.[18, 59]

SPLEEN PATHOLOGY. The spleen is uniformly markedly enlarged in leukemic reticuloendotheliosis. In our single case, it weighed 1220 gm. In Burke's review, the average weight of the spleen was 1809 gm, with a range of 350 to 4650 gm.[18] The capsule may be thickened focally because of underlying infarcts. The cut surface is meaty, dark-red, and

rather homogenous with inconspicuous white pulp. We did not observe gross tumor nodules and none were seen in Burke's cases.[18]

The microscopic picture is rather distinctive. The white pulp is atrophic but of normal architecture and cellular composition. The red pulp is extensively infiltrated with bland, monotonous, mononuclear cells resulting in marked cordal widening. Sinusoids are filled and distended with similar cells and thus, because of cordal and sinusoidal involvement of the red pulp, its basic architecture is obliterated. There is conspicuous absence of pleomorphism and mitoses in this cellular infiltrate, a feature also emphasized by other observers.[18, 108] In massively enlarged spleens there may be partial obliteration of the white pulp as well.[18] The pattern of the infiltration of the spleen is quite unlike that of other lymphomas, which principally affect the white pulp and expand in a nodular fashion into the red pulp without obliterating it. The characteristic pattern and histology of the spleen in leukemic reticuloendotheliosis has been considered pathognomonic of the disease.[18, 59] The suggestion has been made that the red pulp involvement reflects the filtration of circulating "hairy cells" by the spleen.[59]

Malignant Lymphomas

Dramatic and exciting progress has been made in the diagnosis, treatment, and understanding of Hodgkin's disease and, to a lesser degree, other malignant lymphomas, during the last decades. In 1966 Rappaport proposed a classification of non-Hodgkin's lymphomas which has been shown to be of prognostic significance.[82] The modified Lukes and Butler classification of Hodgkin's disease[66] (Rye Classification) has been shown to correlate better with a patient's course than previous classifications. Staging laparotomies in Hodgkin's disease have provided help in defining the extent of disease, thus allowing more optimal therapy.[40]

SPLEEN PATHOLOGY. The spleens involved by malignant lymphoma may be of enormous size, tending to be larger in non-Hodgkin's lymphomas than in Hodgkin's disease. Skarin et al.,[91] in a series of non-Hodgkin's lymphomas, recorded an average weight of 1760 gm, with a range of 550 to 4500 gm; Ahmann[2] recorded an average weight of 1528 gm, with a range of 160 to 5100 gm. In Glatstein's series of Hodgkin's disease, involved spleens ranged in weight from 100 to 1300 gm, spleens weighing more than 400 gm always being involved by Hodgkin's disease.[34] In our and others' experiences a spleen of over 400 gm in a patient with Hodgkin's disease is, rarely, not involved by the disease.[31] Spleens of normal size and weight may be involved by Hodgkin's disease. The clinical, radiologic, and scintographic assessment of splenic size correlate poorly with the actual weight of such spleens.[72] In our experience, 20 spleens involved by Hodgkin's averaged 440 gm (range 125 to 1450 gm).

The capsules of lymphoma-involved spleens may be smooth or focally thickened. It may be bulging because of underlying tumor masses. In our experience there are four distinctive types of gross splenic involvement by malignant lymphomas. (1) The spleen may be

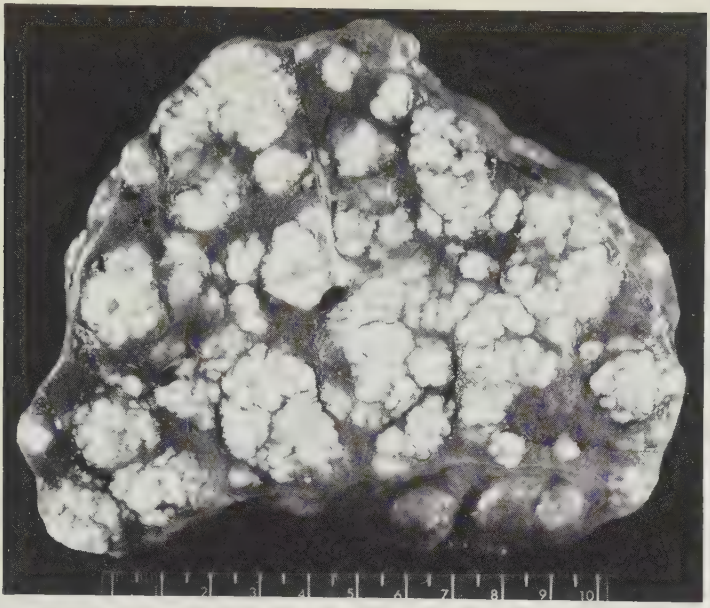

Figure 3. Hodgkin's disease in the spleen. Note the tumor nodules of varying size.

homogenously gray to red-brown on cut section without any discernible masses. Microscopically, such involvement may show any one of histologic types of lymphomas, though Hodgkin's disease in such spleens is rare. (2) The second gross pattern is the miliary pattern in which the spleen is diffusely and uniformly studded with small gray-yellowish tumor nodules varying from 1 to 5 mm in diameter. Again, any histologic type of lymphoma may present such a pattern. (3) The third gross pattern of splenic involvement by malignant lymphoma shows small and large gray-yellow, well circumscribed nodules. The larger nodules usually consist of compact masses of smaller nodules (Fig. 3). This pattern of gross involvement is usually seen with histiocytic lymphomas and Hodgkin's disease. (4) The fourth, and least common pattern, is that of a single small or large tumor mass, a pattern usually only seen with Hodgkin's disease or histiocytic lymphomas involving the spleen. Similar gross types of involvement are described by others.[1, 2]

The malignant lymphomas first and primarily involve the periarterial lymphatic sheaths and lymphoid follicles. These are gradually replaced by the proliferating malignant lymphomas. In the spleen, the neoplastic cells tend to expand in a nodular fashion, compressing and encroaching upon the surrounding red pulp without destroying it. In accompanying lymph nodes from the same patient, such nodularity is frequently not evident,[82] implying that the nodular pattern of the neoplasm in the spleen may be a result of the splenic microenvironment

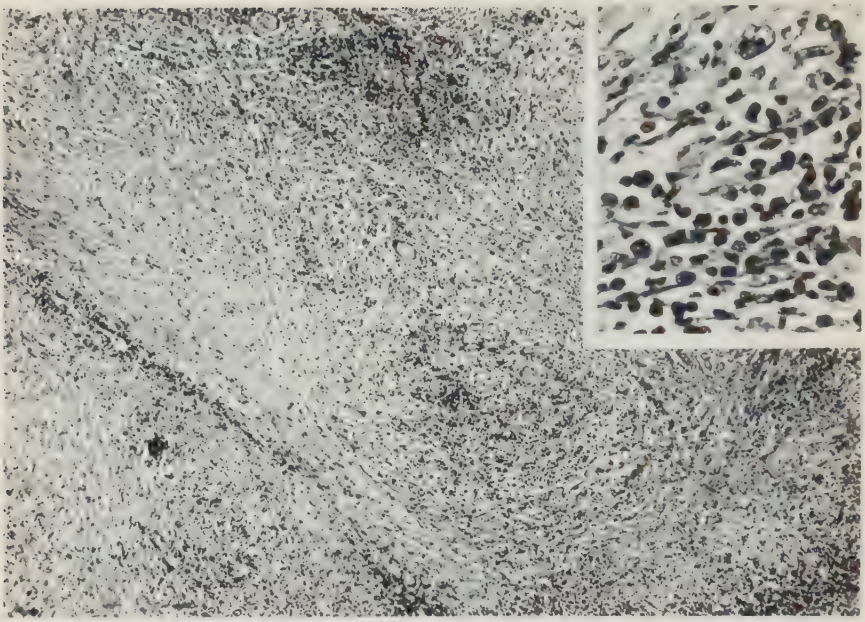

Figure 4. Microscopic picture of the spleen shown in Figure 3. Note replacement of spleen by nodular sclerosing Hodgkin's disease. Hematoxylin-eosin; × 90. Inset shows typical Reed-Sternberg cell seen in the same area. Hematoxylin-eosin; × 470.

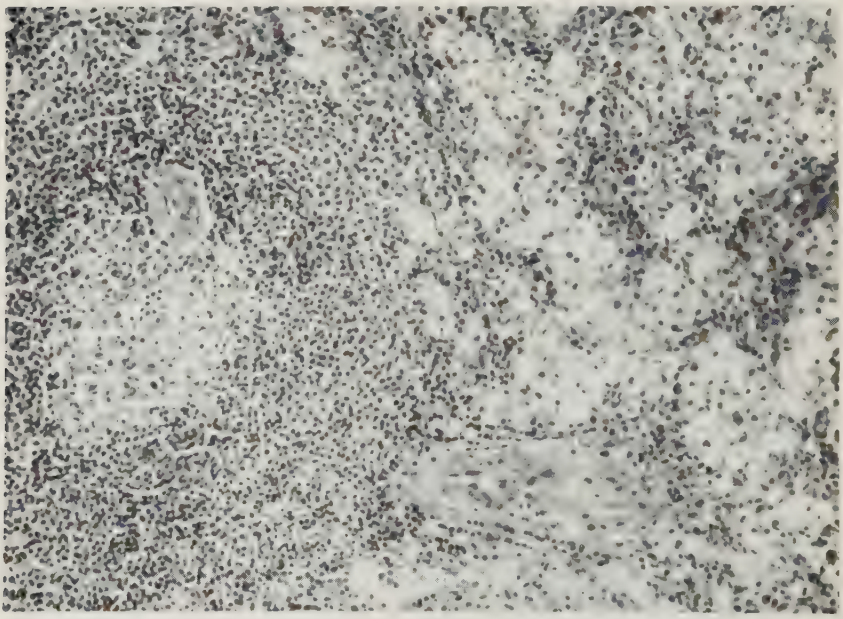

Figure 5. Numerous pale storage cells occupy most of the splenic red pulp. A lymphoid nodule with its germinal center and central arteriole is not affected by the storage cells. Hematoxylin-eosin; × 200.

rather than the inherent growth pattern of the neoplasm. Neoplastic nodules frequently bear no relationship to central arteries or arterioles. In late stages of splenic involvement, the entire microscopic architecture of red and white pulp may be obliterated by tumor. Areas of hemorrhage and necrosis may be frequent.

It is of importance to again emphasize that, particularly in Hodgkin's disease, the splenic involvement may be confined to one focus which may be microscopic or barely visible to the naked eye. This necessitates a careful approach to the examination of spleens, which must be sliced at 2 mm intervals with sampling of any suspicious areas for microscopic examination.

SPHINGOLIPIDOSES THAT PRODUCE SPLENIC ENLARGEMENT

Gaucher's Disease

The sphingolipid disorder that commonly affects the spleen is Gaucher's disease. This disease is an inherited defect of membrane catabolism that results in widespread storage of glucocerebroside in reticuloendothelial cells. There are two forms of the disease, an adult chronic form and a fatal infantile variety.

In 1965 Brady[14] described an enzymatic defect in patients with Gaucher's disease that involved a step in the degradation of membrane lipids. The reduced activity of glucocerebrosidase results in an accumulation of the lipid that cannot be further degraded.

Pathogenesis. As the constant turnover of membrane continues to add more deposits to the body storage sites, the spleen slowly enlarges, to accommodate the increasing numbers of Gaucher's cells. This may result in hypersplenism, with the platelets most commonly affected. Another mechanism of blood cell reduction can occur when the bone marrow is replaced by Gaucher cells and this can result in bleeding, infection, or severe anemia.

Diagnosis. The diagnosis of Gaucher's disease can be made by finding Gaucher cells in the bone marrow, and formerly this was the most frequent method of diagnosis.

In 1970, Beutler[7] described a fluorimetric assay using an artificial substrate that measures the beta-glucosidase activity and permits us to diagnose the disease by finding low activity in blood leukocytes. In addition, the carrier state can also be diagnosed in individuals having enzyme activity intermediate between the low values of a patient with Gaucher's disease and a normal control. Brady has reported that infants having the fatal infantile form of the disease have values of enzyme lower than those with the adult form of the disease.

Gross and Microscopic Pathology. The enlarged spleen is generally homogenous on its cut surface. Occasional small infarcts may produce abdominal pain. Several of our cases have had fibrous nodules measuring up to 4.0 cm in diameter. These are considered to be secondary to vascular alterations that result in focal fibrosis. Angiographic

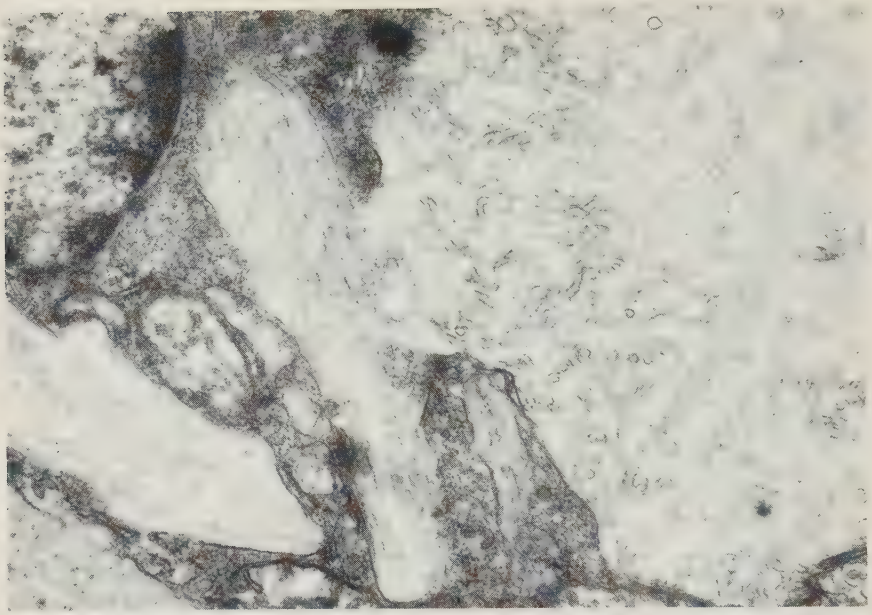

Figure 6. This electron micrograph shows several lysosomes that are distended with the typical twisted deposits of Gaucher's disease. Both longitudinal and cross sectional views of the deposits are present. A portion of nucleus is present in the upper left and two mitochondria are present. Magnification 44,000 ×.

studies of spleens with these nodules have shown patterns resembling hemangiomas. Other types of nodules have been observed to be nodules of extramedullary hematopoiesis, probably secondary to marrow replacement by Gaucher cells. The striated appearance of the Gaucher cells is related to the linear deposits in lysosomes. These deposits are made up of long, narrow, 60Å wide bilayers that twist in a right-handed screw sense. The electron microscopic appearance of tubules when viewed on end is one of a hollow tubule, but freeze-etching and x-ray diffraction studies support a bilayer arrangement of the deposits.[63] The hollow appearance seen in the end view of embedded deposits apparently derives from the extremely compact nature of the multiple bilayers that do not permit aqueous stains to penetrate between the bilayers. The elevated levels of serum acid phosphatase are considered to be related to the release of lysosomal contents as Gaucher cells turn over.

Gaucher cells may appear wherever reticuloendothelial cells are located. This includes such major sites as the red pulp of the spleen and within the bone marrow, but other sites include liver and lymph nodes. Impairment of liver function and lymphadenopathy are not usually observed to be associated with these deposits.

Niemann-Pick Disease

Niemann-Pick disease is another of the sphingolipid storage diseases where the enzymatic defect affects the turnover of sphingomye-

lin. These patients are most commonly infants that exhibit both central nervous system and visceral deposits of this phosphorylated lipid. The storage cells that occur in the spleen and liver have a foamy cytoplasm in contrast to the striated appearance of Gaucher cells. We have seen an adult with Niemann-Pick disease who had splenomegaly that was not detected until he fractured his ribs in an automobile accident. The spleen was removed because of hemorrhage. When the spleen was analyzed, excess amounts of sphingomyelin and cholesterol were found. The electron microscopy of this patient's spleen, liver and bone marrow revealed whorled electron deposits described by Lynn and Terry as typical of Niemann-Pick disease.[67] This patient has no symptoms related to the disease.

Generalized Gangliosidosis-Lactosylceramidosis

We have not seen splenomegaly associated with ganglioside storage although it is reported to occur in generalized gangliosidosis. Here, the storage cells appear to contain large vacuoles that are different from Gaucher's disease or Niemann-Pick disease.[77] Dawson reported on a patient with visceral deposits of ganglioside.[28]

SUMMARY

We have discussed a wide variety of hematologic disorders in which the spleen plays a crucial role. The pathologic changes of the spleen in a number of hemolytic anemias are rather similar. This is not surprising in view of the filtering and culling function of the spleen in these diseases. The pathologic changes seen in the spleen involved by malignant lymphomas are varied. The focal nature of Hodgkin's disease involving the spleen necessitates a careful examination of the spleen so that a small focus of disease is not missed.

REFERENCES

1. Ackerman, L. V., and Rosai, J.: Surgical Pathology, 5th ed. St. Louis, The C. V. Mosby Co., 1974, p. 994.
2. Ahmann, D. L., Kiely, J. M., Harrison, E. G., et al.: Malignant lymphoma of the spleen. Cancer, *19*:461–469, 1966.
3. Amorosi, E. L., and Ultmann, J. E.: Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine, *45*:139–159, 1966.
4. Aster, R. H.: Pooling of platelets in the spleen; role in the pathogenesis of "hypersplenic thrombocytopenia." J. Clin. Invest., *45*:645–657, 1968.
5. Aster, R. H., and Keene, W. R.: Sites of platelet destruction in idiopathic thrombocytopenic purpura. Brit. J. Haematol., *16*:61–73, 1969.
6. Baldini, M.: Idiopathic thrombocytopenic purpura. New Engl. J. Med., *274*:1245–1251; 1301–1306; 1360–1367, 1966.
7. Beutler, E., and Kuhl, W.: The diagnosis of the adult type of Gaucher's disease and its carrier state by demonstration of deficiency of glucosidase activity in peripheral blood leuckocytes. J. Lab. Clin. Med., *76*:747–755, 1970.
8. Bjorkman, S. E.: The splenic circulation. Acta Med. Scand., Suppl., *191*:3–89, 1947.
9. Blackburn, E. K., Jordan, A., Lytle, W. J., et al.: Hereditary elliptocytic haemolytic anemia. J. Clin. Path., *11*:316–320, 1958.
10. Blaustein, A. U., and Diggs, L. W.: Pathology of the spleen. *In* Blaustein, A., ed.: The Spleen. New York, McGraw-Hill Book Co., 1963, pp. 70–75.

11. Bouroncle, B. A., and Doan, C. A.: Myelofibrosis: Clinical, hematologic and pathologic studies of 110 patients. Amer. J. Med. Sci., *243*:697–715, 1962.
12. Bouroncle, B. A., and Doan, C. A.: Cooley's anemia: Indications for splenectomy. Ann. N. Y. Acad. Sci., *119*:709–721, 1964.
13. Bowman, H. E., Pettit, V. D., Caldwell, F. T., et al.: Morphology of the spleen in idiopathic thrombocytopenic purpura. Lab. Invest., *4*:206–216, 1955.
14. Brady, R. O., Kanfer, J. N., and Shapiro, D.: Metabolism of glucocerebrosides. II. Evidence of an enzymatic deficiency in Gaucher's disease. Biochem. Biophys. Res. Commun., *18*:221, 1965.
15. Breckenridge, R. T., Moore, R., and Ratnoff, O. D.: A study of thrombocytopenia. Blood, *30*:39–53, 1967.
16. Burke, J. S., and Simon, G. T.: Electron microscopy of the spleen: II. Phagocytosis of colloidal carbon. Amer. J. Path., *58*:157–181, 1970.
17. Burke, J. S., and Simon, G. T.: Electron microscopy of the spleen: I. Anatomy and microcirculation. Amer. J. Path., *58*:127–155, 1970.
18. Burke, J. S., Byrne, G. E., and Rappaport, H.: Hairy cell leukemia (leukemic reticuloendotheliosis). Cancer, *33*:1399–1410, 1974.
19. Canham, P. B., and Burton, A. C.: Distribution of size and shape in populations of normal human red cells. Circ. Res., *22*:405–422, 1968.
20. Charache, S., Conley, C. L., Waugh, D. F., et al.: Pathogenesis of Hemolytic Anemia in Homozygous Hemoglobin C Disease. J. Clin. Invest., *46*:1795–1811, 1967.
21. Crosby, W. H.: Siderocytes and the spleen. Blood, *12*:165–170, 1957.
22. Crosby, H.: Normal functions of the spleen relative to red blood cells: A Review. Blood, *14*:399–408, 1959.
23. Crosby, W. H.: Current concepts: Splenectomy in hematologic disorders. New Engl. J. Med., *286*:1252–1254, 1972.
24. Cutting, H. O., McHugh, W. T., Conrad, F. G., et al.: Autosomal dominant hemolytic anemia characterized by ovalocytosis. Amer. J. Med., *39*:21–34, 1965.
25. Dacie, J. V.: The Haemolytic Anemias, Congenital and Acquired, Part II. The autoimmune Haemolytic Anemias. 2nd ed., New York, Grune and Stratton, 1962.
26. Dacie, J. V.: The Haemolytic Anemias, Congenital and Acquired Part III. Secondary or Symptomatic Haemolytic Anaemias. New York, Grune and Stratton, 1967.
27. Dameshek, W.: Hypersplenism. Bull. N. Y. Acad. Med., *31*:113–136, 1955.
28. Dawson, G., Matalon, R., and Stein, A. O.: Lactosylceramidosis: Lactosylceramide galactosyl hydrolase deficiency and accumulation of lactosylceramide in cultured skin fibroblasts. J. Pediat., *79*:423 (Sept.) 1971.
29. Diggs, L. W., Kraus, A. P., Morrison, D. B., et al.: Intra-erythrocytic crystal in a white patient with hemoglobin C in the absence of other types of hemoglobin. Blood, *9*:1172–1184, 1954.
30. Doan, C. A.: Hypersplenism. Bull. N. Y. Acad. Med., *25*:625–650, 1949.
31. Farrer-Brown, G., Bennett, M. H., Harrison, C. U., et al.: The pathological findings following laparotomy in Hodgkin's disease. Brit. J. Cancer, *25*:449–457, 1971.
32. Feldman, J. D., Mardiney, M. R., Unanue, E. R., et al.: The vascular pathology of thrombotic thrombocytopenic purpura: An immunohistochemical and ultrastructural study. Lab. Invest., *15*:927–946, 1966.
33. Firkin, B. G., Wright, R., Miller, S., et al.: Splenic macrophages in thrombocytopenia. Blood, *33*:240–245, 1969.
34. Glatstein, E., Guernsey, J. M., Rosenberg, S. A., et al.: The value of laparotomy and splenectomy in the staging of Hodgin's disease. Cancer, *24*:709–718, 1969.
35. Gomperts, E. D., Cayannis, F., Metz, J., et al.: Red cell membrane protein abnormality in hereditary elliptocytosis. Brit. J. Haematol., *25*:415–420, 1973.
36. Gore, I.: Disseminated arteriolar and capillary platelet thrombosis: A morphological study of its histogenesis. Amer. J. Path., *26*:155–175, 1950.
37. Green, T. W., Conley, L., Ashburn, L. L., et al.: Splenectomies for myeloid metaplasia of the spleen. New Engl. J. Med., *248*:211–219, 1953.
38. Handin, R., Smith, A.: Immunopathic or immunogenic thrombocytopenic purpura. (Editorial.) New Engl. J. Med., *286*:720–721, 1972.
39. Harrington, W. J., Minnich, V., Hollingsworth, J. W., et al.: Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. J. Lab. Clin. Med., *38*:1–10, 1951.
40. Hellman, S.: Current studies in Hodgkin's disease. New Engl. J. Med., *290*:894–898, 1974.
41. Hickling, R. A.: Chronic non-leukemic myelosis. Quart. J. Med., *6*:253–275, 1937.
42. Hill, J. B., and Cooper, W. M.: Thrombotic thrombocytopenic purpura. Treatment with corticosteroids and splenectomy. Arch. Intern. Med., *122*:353–356, 1968,
43. Hirasawa, Y., and Tokuhiro, H.: Electron microscopic studies on the normal human spleen: Especially on the red pulp and the reticuloendothelial cells. Blood, *35*:201–212, 1970.

44. Huber, H., Polley, M. L., Linscott, W. E., et al: Human monocytes: Distinct receptor sites for the third component of complement and for immunoglobulin G. Science, *162*: 1281–1283, 1958.
45. Hunt, J. A., and Ingram, V. M.: Allelomorphism and the chemical differences of human hemoglobin A, S, and C. Nature, *181*:1062–1063, 1958.
46. Jackson, H., Parker, E., and Lemon, H. M.: Agnogenic myeloid metaplasia of the spleen: Syndrome simulating other more definite hematologic disorders. New Engl. J. Med., 222:985–994, 1940.
47. Jacob, H. S., and Karnovsky, M. L.: Concomitant alterations of sodium flux and membrane phospholipid metabolism in the red blood cells: Studies in hereditary spherocytosis. J. Clin. Invest., *46*:173–185, 1967.
48. Jacob, H. S.: The defective red blood cell in hereditary spherocytosis. Ann. Rev. Med., *20*:41–46, 1969.
49. Jacob, H. S.: Hypersplenism. *In* Williams, W. J., Beutler, E., Erslev, A. J., and Rundles, R. W., eds.: Hematology. New York, McGraw-Hill Book Co., 1972, pp. 511–520.
50. Jacob, H. S.: The abnormal red cell membrane in hereditary spherocytosis: Evidence for the causal role of mutant microfilaments. Brit. J. Haematol., *23* (Suppl.):35–44, 1972.
51. Jacob, H. S.: Hypersplenism: Mechanisms and management. Brit. J. Haematol., *27*:1–5, 1974.
52. Jandl, J. H., Simmons, R. L., and Castle, W. B.: Red cell filtration in the pathogenesis of certain hemolytic anemias. Blood, *18*:133–148, 1961.
53. Jandl, J. H., Files, N. M., Barnett, S. B., et al.: Proliferative response of the spleen and liver to hemolysis. J. Exper. Med., *122*:299–327, 1965.
54. Jandl, J. H., and Aster, R. H.: Increased splenic pooling and the pathogenesis of hypersplenism. Amer. J. Med. Sci., *253*:383–398, 1967.
55. Jensen, W. N., and Lessin, L. S.: Membrane alterations associated with hemoglobinopathies. Semin. Hematol., 7:409–426, 1970.
56. Kadin, M. E., Glatstein, E., and Dorfman, R. F.: Clinicopathologic studies of 117 untreated patients subjected to laparotomy for staging of Hodgkin's disease. Cancer, *27*:1277–1294, 1971.
57. Karpatkin, S., and Siskind, G. W.: In vitro detection of platelet antibody in patients with idiopathic thrombocytopenic purpura and systemic lupus erythematosus. Blood, *33*:795–812, 1969.
58. Karpatkin, S.: Idiopathic autoimmune thrombocytopenic purpura. Hosp. Pract., 5:100–109, 1970.
59. Katayama, I., and Finkel, H. E.: Leukemic reticuloendotheliosis. A clinicopathologic study with review of the literature. Amer. J. Med., *57*:115–126, 1974.
60. Kirkegaard, A., and Larsen, K.: Elliptische Erythrocyten in einer dänischen Familie and einige Untersuchungen über die Natur der Elliptocytose. Acta Med. Scand., *110*:521–547, 1942.
61. Krumbhaar, E. B., and Lippincott, S. W.: The postmortem weight of the "normal" human spleen at different ages. Amer. J. Med. Sci., *197*:344–358, 1939.
62. Lawson, N. S., and Smith, E. B.: Splenic ultrastructure in rats treated with methylcellulose. Arch. Path., *85*:179–188, 1968.
63. Lee, R. E., Worthington, C. R., and Glew, R. H.: The bilayer nature of the membranous deposits occurring in Gaucher's disease. Arch. Biochem. Biophys., *159*:259–266 (Nov.) 1973.
64. Lipton, E. L.: Elliptocytosis with hemolytic anemia: The effects of splenectomy. Pediatrics, *15*:67–83, 1955.
65. LoBuglio, A. F., Cotran, R. S., and Jandl, J. H.: Red cells coated with immunoglobulin G: Binding and sphering by mononuclear cells in man. Science, *158*:1582–1585, 1967.
66. Lukes, R. J., et al.: Report of the Nomenclature Committee. Cancer Res., 26:1311, 1966.
67. Lynn, R., and Terry, R. D.: Lipid histochemistry and electron microscopy in adult Niemann-Pick disease. Amer. J. Med., *37*:987, 1964.
68. McCormick, W. G., and Kashgarian, M.: The weight of the adult human spleen. Amer. J. Clin. Path., *43*:332–333, 1965.
69. McMillan, R., Longmire, R. L., Yelenosky, R., et al.: Immunoglobulin synthesis in vitro by splenic tissue in idiopathic thrombocytopenia purpura. New Engl. J. Med., 286:681–684, 1972.
70. Meacham, G. C., Orbinson, J. L., Heinle, R. W., et al.: Thrombotic thrombocytopenic purpura: A disseminated disease of arterioles. Blood, 6:706–719, 1951.
71. Molnar, Z., and Rappaport, H.: The fine structure of the red pulp of the spleen in hereditary spherocytosis. Blood, *39*:81–98, 1972.
72. Moran, E. M., and Ultman, J. E.: Clinical features and course of Hodgkin's disease. Clin. Haematol., 3:91–129, 1974.
73. Morton, N. E.: The detection and estimation of linkage between genes for elliptocytosis and the Rh blood type. Amer. J. Hum. Genet., *8*:80–96, 1956.

74. Mukherjee, A. M., Sen Gupta, P. C., and Chatterjea, J. B.: The Spleen in Thalassemia. J. Indian Med. Assoc., 33:451–468, 1959.
75. Murphy, J. R.: The influence of pH and temperatures on some physical properties of normal erythrocytes and erythrocytes from patients with hereditary spherocytosis. J. Lab. Clin. Med., 69:758–775, 1967.
76. Nickerson, D. A., and Sunderland, D. A.: The histopathology of idiopathic thrombocytopenic purpura hemorrhagica. Amer. J. Path., 13:463–490, 1937.
77. O'Brien, J.: Generalized gangliosidosis. J. Pediat., 75:167, 1969.
78. Orbison, J. L.: Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms. Amer. J. Path., 28:129–143, 1952.
79. Parker, R. C.: Studies on the production of antibodies in vitro. Science, 85:292–294, 1937.
80. Pitcock, J. A., Reinhard, E. H., Justus, B. W., et al.: A clinical and pathologic study of 70 cases of myelofibrosis. Ann. Intern. Med., 57:73–84, 1962.
81. Rappaport, H., and Crosby, W. H.: Autoimmune hemolytic anemia. II. Morphologic observations and clinicopathologic correlation. Amer. J. Path., 33:429–457, 1957.
82. Rappaport, H.: Tumors of the hematopoietic system. *In* Atlas of Tumor Pathology, Section III, Fascicle 8, Armed Forces Institute of Pathology, Washington, D.C., 1966.
83. Rifkind, R. A.: Heinz body anemia: An ultrastructural study. II. Red cell sequestration and destruction. Blood, 26:433–448, 1965.
84. Saltzstein, S. L.: Phospholipid accumulation in histiocytes of the splenic pulp associated with thrombocytopenic purpura. Blood, 18:73–88, 1961.
85. Schnitzer, B., Soderman, T., Mead, M. L., et al.: Pitting functions of the spleen in malaria: Ultrastructural observations. Science, 177:175–177, 1972.
86. Schnitzer, B., and Kass, L.: Hairy-cell leukemia, a clinicopathologic and ultrastructural study. Amer. J. Clin. Path., 61:176–187, 1974.
87. Schrek, R., and Donnelly, W. J.: "Hairy cells" in blood in lymphoreticular neoplastic disease and "flagellated" cells of normal lymph nodes. Blood, 27:199–211, 1966.
88. Sen Gupta, P. C., Chatterjea, J. B., Mukherjee, A. M., et al.: Observations on the foam cell in thalassemia. Blood, 16:1039–1044, 1960.
89. Shulman, N. R., Marder, V. J., and Weinrach, R. S.: Similarities between known antiplatelet antibodies and the factor responsible for thrombocytopenia in idiopathic purpura: Physiologic, serologic and istopic studies. Ann. N. Y. Acad. Sci., 124:499–542, 1965.
90. Silverstein, M. N., Gomes, M., ReMine, W. H., et al.: Agnogenic myeloid metaplasia—Natural history and treatment. Arch. Intern. Med., 120:546–550, 1967.
91. Skarin, A. T., Davey, F. R., and Moloney, W. C.: Lymphosarcoma of the spleen. Arch. Intern. Med., 127:259–265, 1971.
92. Tavassoli, M., and Weiss, L.: An electron microscopic study of spleen in myelofibrosis with myeloid metaplasia. Blood, 42:267–279, 1973.
93. Umlas, J., and Kaiser, J.: Thrombohemolytic thrombocytopenic purpura (TTP). A disease or a syndrome? Amer. J. Med., 49:723–728, 1970.
94. Videbaek, A.: Autoimmune hemolytic anemia in systemic lupus erythematosus. Acta Med. Scand., 171:187–194, 1962.
95. Von Haam, E., and Awny, A. J.: The pathology of hypersplenism. Amer. J. Clin. Path., 18:313–322, 1948.
96. Ward, H. P., and Block, M. H.: The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. Medicine, 50:357–420, 1971.
97. Weed, R. I., and Reed, C. F.: Membrane alterations leading to red cell destruction. Amer. J. Med., 41:681–698, 1966.
98. Weed, R. I., and Weiss, L.: The relationship of red cell fragmentation occurring within the spleen to cell destruction. Trans. Assoc. Amer. Physicians, 79:426–438, 1966.
99. Weiss, L., and Tavassoli, M.: Anatomical hazards to the passage of erythrocytes through the spleen. Semin. Hematol., 7:372–380, 1970.
100. Weiss, L.: Spleen. *In* Greep, R. O., and Weiss, L., eds.: Histology, 3rd ed. New York, McGraw-Hill Book Co., 1973, pp. 445–476.
101. Wennberg, E., and Weiss, L.: Splenomegaly and hemolytic anemia induced in rats by methylcellulose—An electron microscopic study. J. Morphol., 122:35–62, 1967.
102. Wennberg, E., and Weiss, L.: Splenic erythroclasia: An electron microscopic study of hemoglobin H disease. Blood, 31:778–790, 1968.
103. Wheby, M. S., Thorup, O. A., and Leawell, B. S.: Homozygous hemoglobin C disease in siblings: further comment on intraerythrocytic crystals. Blood, 11:266, 272, 1956.
104. Wiland, O. K., and Smith, E. B.: The morphology of the spleen in congenital hemolytic anemia (congenital spherocytosis). Amer. J. Clin. Path., 26:619–629, 1956.
105. Williams, G. M., and Nossals, G. J. V.: Ontogeny of the immune response. I. The development of follicular antigen trapping mechanism. J. Exper. Med., 124:47–56, 1966.

106. Wilson, H. E., and Long, J. J.: Ovalocytosis with hypersplenism: Report of two cases and observations on the pathogenesis of the hyperspleniam. (Abstract.) Amer. J. Med., *14*:534, 1953.
107. Yam, L. T., Li, C. Y., and Lam, K. W.: Tartrate resistant acid phosphatase isoenzyme in the reticulum cells of leukemic reticuloendotheliosis. New Engl. J. Med., *284*:357–360, 1971.
108. Yam, L. T., Li, C. Y., and Finkel, H. E.: Leukemic reticuloendotheliosis—The role of tartrate-resistant acid phosphatase in diagnosis and splenectomy in treatment. Arch. Intern. Med., *130*:248–256, 1972.

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Hematologic Indications for Splenectomy

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The role of splenectomy in the management of various hematologic disorders has grown in importance over the past 25 years. This increase in popularity is mainly due to our better understanding of these disease states and a better clarification of the indications for this procedure. The pathophysiology of the spleen has been more clearly elucidated through many investigative studies during the century. Thus, its importance in cellular sequestration and destruction along with its place in immunologic mechanisms is better understood although not fully clarified. A number of reviews depicting the hematologic indications for splenectomy have appeared in the literature in recent years.[23, 40, 53, 62, 111, 112, 114, 122]

The current presentation addresses autoimmune hematologic disorders, congenital hemolytic states, thrombotic thrombocytopenic purpura, staging procedures for "lymphomas," and, ultimately, miscellaneous indications for splenectomy. Hypersplenism, of both primary and secondary types, is an important indication for splenic removal. Although a few of the included topics display features characteristic of this syndrome, this interesting subject is discussed in another article included in this symposium.[48]

AUTOIMMUNE DISORDERS

Autoimmune Hemolytic Anemia (AIHA)

The immune hemolytic anemias are classified on the basis of the absence or presence of an underlying medical disorder, or upon the associated serologic characteristics of the immune process.[125] The initial classification separates these entities into "idiopathic" versus "secondary" or "symptomatic" cases. The secondary causes primarily include

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the lymphoproliferative disorders and the collagen disease states, particularly systemic lupus erythematosus. Other causes are shown in Table 1. Dacie[26] points out that the longer patients are followed, the greater the likelihood exists for the appearance of an additional underlying condition. Pirofsky[98] suggests that autoimmunization rarely affects the red cells alone.

Secondarily, these disorders may be classified according to the variant of antibody produced, namely so called "warm" versus "cold" types. The characteristics of these antibodies are depicted in Table 2, and three clinical syndromes can be distinguished related to these antibody differences.

Of major interest and importance to the surgeon is the hemolytic syndrome associated with warm antibody production. It is this variant that almost exclusively leads to splenectomy. In the other two entities, cold hemagglutination syndrome and paroxysmal cold hemoglobinuria, splenectomy is rarely considered. Therefore, the majority of the remaining discussion will focus on the syndrome associated with warm antibody production.

Warm Antibody Syndrome

The idiopathic form of the warm antibody syndrome has a variable age of onset, but is infrequently seen in children. Females have approximately twice the incidence of males. The onset of the disease may be acute, accompanied by abrupt hemolysis with varying degrees of anemia noted. At times, the acute onset is associated with severe dyspnea, fever, and a shock-like state with coma, possibly resulting in death. In contrast, the insidious chronic form may be present for many years, associated with mild anemia, undue fatigue, and mild dyspnea on exertion. The patient may note symptoms related only to the anemia, but occasionally jaundice and thrombophlebitis may occur.

On physical examination, the affected individual generally shows pallor, mild jaundice with scleral icterus, and frequently palpable splen-

Table 1. *Classification of AIHA by Underlying Disorders*

PRIMARY OR "IDIOPATHIC" CASES
SECONDARY OR "SYMPTOMATIC" CASES
Lymphoproliferative disorders (chronic lymphatic leukemia; lymphomas)
Collagen diseases (systemic lupus erythematosus; rheumatoid arthritis)
Benign tumors (dermoid cysts; teratomas, particularly ovarian)
Myeloproliferative disorders
Carcinomas
Infectious causes (Mycoplasma; infectious mononucleosis)
Granulomatous disease (tuberculosis; sarcoidosis)
Chronic disease states (ulcerative colitis; liver disease)
Thyrotoxicosis
Drugs (Aldomet, prime offender)

Table 2. *Characteristics of Autoantibodies in AIHA*

	WARM TYPE	COLD TYPES	
	Warm Antibody Syndrome	Cold Hemagglutinin Syndrome	Paroxysmal Cold Hemoglobinuria
Immunoglobulin class and size	IgG (7S)	IgM (19S)	IgG (7S)
Thermal reactivity Initial Maximal	37° C	28–32° C 0–4° C	15–20° C 0–4° C
Antigenic specificity		I; i	P (red cell membrane antigen)
Complement fixation	Usually Absent	+	+
Agglutination (in vitro activity)	Incomplete	Complete (High titer at 4° C)	Generally poor (Moderate titer at 4° C)
Hemolysis (in vivo activity)	Spherocytosis with hemolysis	Agglutination and lysis	Spherocytosis and lysis
Typical Coombs reaction	Gamma (IgG)	Non-gamma (C_3)	Non-gamma (C_3) (with acute episode)
Destruction	Primarily spleen	Primarily liver	Primarily intravascular and liver
Splenectomy	Of value	Rarely of value	Of no value

omegaly. In addition, hepatomegaly may be present along with lymphadenopathy, at times suggestive of an underlying lymphoproliferative disorder. Cyanosis may be seen in very severe forms[28] secondary to intravascular autoagglutination.

Laboratory data are important in helping to differentiate the primary and secondary types of AIHA, as well as in excluding other hemolytic states.

TREATMENT. Treatment of warm antibody type hemolytic anemia will depend on the ultimate classification of the disorder into either an "idiopathic" or a "secondary" type. Associated secondary disease states must be carefully sought and appropriately treated. If no underlying disorder can be found, treatment should be begun in an attempt to abate the primary hemolytic process.

Generally, the initial therapy is corticosteroids. Steroids produce beneficial effects in approximately 75 per cent of those treated, with red blood counts often returning to normal as the hemolysis decreases. Unfortunately, when the drug is discontinued, many patients suffer a relapse of the hemolytic process.[28]

When steroid therapy fails, one must then consider splenectomy or

immunosuppressive therapy. It has generally been our policy to recommend splenectomy in idiopathic cases which fail to respond in 4 to 6 weeks of high dose steroid therapy, and in patients with relapse after initial response, when steroid therapy is tapered or withdrawn. In addition to being of value therapeutically, splenectomy may establish a diagnosis of an underlying primary disorder, such as lymphoma.

Prior to splenectomy, it is of value to have the patient undergo a Cr-51 red cell survival and splenic sequestration study to help predict a favorable response to this procedure.[60] The major significance of these studies is to evaluate the ratio of splenic : liver sequestration of the labelled red cells. A spleen : liver ratio of 2 to 3 : 1 or more usually predicts a favorable response. Occasionally, splenectomy has been of value with normal spleen : liver ratios, and decreased need for transfusions and high dose steroid therapy has followed.

Other early indications for splenectomy include toxic manifestations of steroid treatment or contraindications for their use, such as active pulmonary tuberculosis, peptic ulcer disease, etc. We have more enthusiasm for splenectomy than others because of the serious consequences of long term steroid therapy especially in high dosage.

Splenectomy[126] in AHIA tends to provide better results in patients with: (1) warm antibodies, especially with low titers; (2) positive direct but not indirect Coombs tests; (3) no cold agglutinins or complement-fixing antibodies; and (4) splenic enlargement with selective sequestration demonstrated by Cr-51 studies.[3] A favorable response to splenectomy can be anticipated in 50 to 80 per cent of cases, although relapses are not infrequent.

A third therapeutic approach is the use of antimetabolites, which have been shown to suppress the immune reaction, and Dameshek and Schwartz[33] are credited with their initial use after failure of splenectomy and steroids. This group of agents has not yet been critically evaluated, and the relatively high dosage required along with their known side effects is of concern.

Transfusion therapy is best avoided in this disease unless absolutely necessary. Cross matching is difficult and further antibody production secondary to incompatible antigens augments the problem.

The prognosis is relatively good in the idiopathic cases, but the disease may assume a chronic form. In secondary cases, the prognosis is dependent on the underlying disorder.

Immunologic Thrombocytopenic Purpura (ITP)

Prior to 1951, immunologic thrombocytopenic purpura was defined as a clinical disorder of unknown etiology associated with (1) thrombocytopenia and purpura, (2) normal or increased megakaryocytes in the bone marrow, and (3) the absence of splenomegaly and other underlying disorders.

Then Harrington in 1951[64] established that an antiplatelet factor

with autoantibody characteristics existed in the serum of many of these patients and, thus, added a new dimension to the diagnosis.

No longer considered a single disorder, immunologic thrombocytopenic purpura reflects a syndrome composed of diverse entities which have a few characteristics in common.[8] One must demonstrate directly or indirectly that a shortened platelet life span exists and that the disease has an "immunologic" pathogenesis in order to establish a correct diagnosis. The disease is not always idiopathic, but may be secondary to other underlying disorders which produce a picture of thrombocytopenia by an autoimmune or allergic process. At times, it is exceedingly difficult to establish whether the disease as it initially presents is truly idiopathic or secondary. Thus, Baldini has suggested that the meaning of ITP should be altered to "immunologic thrombocytopenic purpura." However, confusion has existed with the term when used as a synonym for ITP.[7] Many series have included purpura caused by secondary forms of immune thrombocytopenia, while others[112] reserve the term ITP to describe patients with thrombocytopenia, with normal or increased marrow megakaryocytes, in the absence of an underlying systemic disorder or suggestive drug ingestion history. Dameshek[31] noted the presence of abnormal megakaryocytes in the marrow of patients with this disorder (absence of platelet budding, lack of granulation, vacuolization, etc.), and interpreted this finding to represent a decrease of platelet production by way of a humoral antagonist. Doan[41] suggested that the disorder was secondary to increased platelet destruction by the spleen. Generally, it is now accepted that ITP is caused by increased platelet destruction in the reticuloendothelial system,[64] predominantly by the spleen, and that increased megakaryocyte production and number occur proportionately.

Initially, in the work-up of ITP, it is important to ascertain that the patient affected demonstrates increased platelet destruction secondary to an immunologic process and then to determine if this is idiopathic or secondary in nature. Unfortunately, measurement of platelet life span with radioisotope techniques is still difficult and not readily available in all institutions. The demonstration of antiplatelet antibody in the absence of previous numerous platelet or blood transfusions is important in establishing a diagnosis of an autoimmune state. However, at the present time a practical, sensitive, and well proved serologic test for ITP is not available. Newer serologic antibody techniques have shown a higher percentage of positive confirmatory results suggesting increased sensitivity of these methods; however, negative results are not necessarily reliable.[8] Therefore, the diagnosis of ITP syndrome is often established indirectly by excluding other disorders associated with thrombocytopenia caused by non-immunologic mechanisms (Table 3). Generally, in most patients, the combination of normal or increased marrow megakaryocytes along with peripheral blood thrombocytopenia is caused by increased platelet destruction. Ineffective thrombopoiesis associated with increased megakaryocytes in the marrow, but with a normal platelet life span and peripheral blood thrombocytopenia, is rare. Thereafter, one must determine whether the immunologic process is truly of an idiopathic or secondary nature.

Table 3. *Differential Diagnosis of Immunologic Thrombocytopenic Purpura*

INEFFECTIVE THROMBOCYTOPOIESIS	NON-IMMUNE PLATELET DESTRUCTIVE DISORDERS	IMMUNE PLATELET DESTRUCTION
Pernicious anemia	Septicemia	Idiopathic Forms
Paroxysmal nocturnal hemoglobinuria	Hypersplenism	Acute
Pre-leukemic states	Intracorpuscular platelet defects	Recurrent
DiGuglielmo's syndrome	Disseminated intravascular coagulopathies and associated states	Chronic
		versus
		Secondary Forms
		Systemic lupus erythematosus
		Evan's syndrome
		Lymphoproliferative disorders
		Drug-induced
		Post transfusion

The idiopathic form of immune thrombocytopenia can be classified temporally into acute, chronic, and recurrent types.

The *acute variety* is seen most frequently in children, generally occurring before 8 years of age. Often the onset can be related to an antecedent seasonal (winter-spring) viral illness, rarely occurs after vaccination for a viral disorder, or may be related to drug intake. The infection which commonly precedes the onset of thrombocytopenic purpura by 1 to 3 weeks is usually upper respiratory or secondary to exanthematous childhood illness. In the acute form, the sudden purpuric onset frequently is associated with mucous membrane blood blisters. Marked thrombocytopenia is commonly present. The disease runs a self-limited course averaging 1 to 2 months, but may range from 1 week to 3 to 4 months. Both sexes are equally affected. The disease generally has a favorable prognosis, but 27 deaths have been reported in 709 cases not treated with steroids.[74] The majority of deaths have been secondary to cerebral hemorrhage. Approximately 8 to 10 per cent of the cases may progress to the chronic, self-perpetuating form.

Adults affected with this variety of ITP usually have more severe manifestations than those seen in children. Bleeding from the gastrointestinal tract, hematuria, severe purpura, epistaxis, and central nervous system hemorrhage are more frequent in the adult (this disorder in the adult is often related to drug hypersensitivity, quinidine being most commonly implicated).

Acute ITP occurring several weeks after a viral illness should not be confused with the severe thrombocytopenia at times accompanying an acute viral illness, during the viremic phase. This mechanism is not one of immunologic origin, but reflects a direct effect on platelet agglutina-

tion and destruction along with decreased megakaryocyte production in the marrow.

The *chronic form* characteristically has an insidious onset with an accompanying long history of easy bruisability and, in women, is frequently associated with menorrhagia. Commonly, the platelet count is moderately decreased, usually in the range of 30,000 to 80,000 cu mm. Females clearly display a higher incidence of this variety with a frequency somewhere between 2 to 4 : 1 over males. Clinically, these patients have petechiae and ecchymoses. At times, no other signs are present. Splenomegaly is rarely found and, when present, one must seriously question the diagnosis of an idiopathic form of disease. Other bleeding sites include the gums, vagina, gastrointestinal, or genitourinary tract. Central nervous system bleeding occurs in a low percentage of cases and generally early in the disease. The disease may last for many years with cyclic remissions and exacerbations and is considered a self perpetuating disorder.[8] During remission, the patient is free of purpura, but the platelet counts remain at levels one third to one half normal. On occasions, the disease becomes milder after many years and may entirely disappear. In most cases, the disease is not severe enough to be life threatening, although a mortality of 6.8 per cent in a series of 147 patients[11] has been reported.

Lastly, the *recurrent ITP variety* occurs in a relatively small percentage of patients. Mostly these cases are of an acute variety. Thrombocytopenia lasts from weeks to months spaced with intervals free of active disease with return of normal platelet counts and survival. Subsequently, relapses occur again associated with purpura, thrombocytopenia, and shortened platelet survival.

LABORATORY FINDINGS. Characteristic laboratory findings help to establish the diagnosis. The platelet count is moderately to severely decreased, and this is associated with an increased bleeding time and capillary fragility. Generally, red cell counts are normal, but it is not unusual to find secondary iron deficiency anemia, particularly in women with menorrhagia. Typically, normal white cell counts are present. The bone marrow shows normal or increased numbers of megakaryocytes with secondary qualitative changes, as previously described. The transfusion of ^{51}Cr-labelled normal platelets into patients with ITP discloses a shortened survival time and a relationship between platelet survival and platelet count can be demonstrated.

Treatment

Treatment is dependent on the clinical variant. Secondary cases of immune thrombocytopenia are best managed by appropriate therapy directed against the underlying primary disorder. At times, however, therapy similar to that for the idiopathic cases is instituted in an effort to correct the associated thrombocytopenia.

Therapy in the truly idiopathic forms is dependent on whether the variant is acute or chronic. Generally, the acute form in children is accompanied by an excellent prognosis, as noted above.

In the chronic form of this disease, the major lines of therapy have included corticosteroids, splenectomy, and immunosuppressive agents.

In general, it has been our policy to pursue the following approach in patients with chronic ITP. Initially, high dose corticosteroids in the range of 1 to 1.5 mg per kg per day are given for approximately 4 weeks. Subsequently, we find two major indications for splenectomy: (1) failure of response with lack of return of platelet counts to normal range, and (2) relapse of thrombocytopenia after normal levels are achieved, and steroid dosage is tapered and stopped. Patients who have had a good response to corticosteroids usually respond favorably to splenectomy, but there is no strict correlation between the response to these two modes of therapy. In general, patients with platelet rises above normal levels postoperatively have a better chance of achieving a permanent remission.[125] Splenectomy may be effective in two ways: (1) it removes the major site of platelet sequestration and destruction and (2) removes a major site of antibody production.

Much of the literature supports more procrastination in the management of chronic ITP. Some suggest that splenectomy can be delayed indefinitely as long as platelet counts remain at "safe" levels, i.e., greater than 50,000, with no or low dose steroid management.[74] In our experience, the splenectomy approach has been associated with far fewer complications. Subsequent response rates to splenectomy vary between 50 and 85 per cent dependent upon the series reviewed. Much of the variation reflects differences in the classification of ITP, as noted in the preceding discussion; undoubtedly, truly idiopathic forms have a higher response rate than those secondary to another primary medical disorder.

If corticosteroids and splenectomy fail to achieve a remission or if relapse occurs, immunosuppressive therapy can then be considered. This form of therapy is reserved for the most resistant patients and, therefore, the low response rate of 20 to 30 per cent is not surprising. Recently,[2] vincristine has been reported to be effective in a relatively high percentage of such cases, but more clinical trials are necessary to confirm these findings.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a much discussed autoimmune connective (collagen) tissue disorder characterized by protean manifestations of multisystem involvement. Various hematologic abnormalities are seen with this disease and these may be the presenting features of the illness. Within the scope of this discussion, we are primarily interested in presentations of SLE reflected by immune thrombocytopenia and/or hemolytic anemia.

In some series, warm antibody type AIHA diagnosed in young women between age 10 and 30 results in the diagnosis of SLE in nearly 50 per cent of cases.[29] The serology in hemolytic anemia associated with SLE is unusual and characteristic. The autoantibody has *not* been

shown to be anti-Rh and a component of the antibody fixes complement. Its specificity has not yet been identified.

The role of splenectomy in SLE associated with these immune disorders has been controversial.[12] Initially, it was believed by various writers that splenectomy might lead to a dissemination of latent SLE and this view was supported mainly by Dameshek and his colleagues.[37] The theory proposed by this group was that the spleen exerted a "staying or inhibitory effect" on the lupus process,[32] and secondly, its removal could modify the immunologic behavior within the body, resulting in the sudden activity of a primarily latent lupus process.[30] Thus, they recommended a more conservative approach to these immune entities rather than the precipitous use of splenectomy.

However, against this theory is the concept that SLE is a disease of autoimmunization and the spleen is a major site of immune antibody formation. Thus, the presence of the spleen would have to both aggravate and protect the individual against the lupus process, and this is a difficult concept to accept.[12]

Best and Darling[12] reviewed the world literature and concluded that some individuals who are prone to develop SLE also have the same likelihood to develop immune cytopenia. Temporally, the development of the two may be quite close. However, review of these cases failed to substantiate the claim that splenectomy leads to dissemination of SLE, but on the contrary, its effect has often proved to be quite beneficial. Others have supported Best's conclusions.[42, 85] Doan[42] points out that SLE occurs in 2 per cent of cases with ITP, but in only 1.2 per cent of those patients subjected to splenectomy.

In general, we do not delay splenectomy in a steroid unresponsive ITP or AIHA case, when overt evidence of SLE does not exist. Additionally, we concur that there is no clear cut evidence that splenectomy exerts a deleterious effect on SLE, should it become overt following the procedure. At times, splenectomy is quite valuable in SLE when these immunocytopenias develop in the course of this disorder.

EVANS' SYNDROME[52]

This disorder is mentioned to note the rarity of the association of autoimmune hemolytic anemia and ITP in the same individual. The thrombocytopenia and anemia can occur at the same time or alternately. The etiology may be idiopathic or secondary to another underlying disease, usually lymphoma. The prognosis is generally poor.[29]

CONGENITAL HEMOLYTIC STATES

HEREDITARY SPHEROCYTOSIS

Hereditary spherocytosis (congenital hemolytic jaundice) is a hemolytic disorder with intrinsically abnormal erythrocytes. The disease is

one transmitted with autosomal inheritance. Its Mendelian dominant pattern is generally confirmed through investigation of the afflicted individual's family. The condition may be initially discovered early in infancy or it may escape detection until later in adult life, the highest incidence occurring in the first three decades. It has been described most frequently in people of European origin and is less commonly seen among Negroes.

Etiology and Pathophysiology

Dominant thought in hereditary spherocytosis has been directed toward the nature of the structural and metabolic red cell abnormality along with the spleen's ability to detect this defect, and subsequently lead to the red cell's early destruction. The precise defect remains unknown, but most research supports the concept that the structure of the cell membrane is abnormal[68, 77] and permits an increase of red cell Na^+ permeability.[82] The membrane defect manifests itself by a surface area deficiency which permits the erythrocyte to assume a spheroidal shape. Secondarily, the altered Na^+ flux causes an increase of cellular glucose utilization, resulting in membrane lipid instability. Ultimately, red cell stagnation in the unfavorable splenic pulp environment produces a series of characteristic changes including the loss of membrane and membrane function. This leads to cellular death with eventual erythrophagocytosis occurring. The cells that escape splenic macrophages and reappear in the circulation are now more spherical and rigid, and thus, more likely to be trapped and destroyed during their subsequent splenic passage.[120]

Clinical Features

The essential clinical manifestations of this disorder include anemia, jaundice, and splenomegaly. The degree of anemia and jaundice is generally mild to moderate and is rarely severe. The icterus generally parallels the degree of anemia, as it is related to the red cell destruction with subsequent production of increased levels of unconjugated bilirubin. When the unconjugated bilirubin load presented to the liver exceeds its capacity to conjugate, elevated serum bilirubin levels occur with subsequent jaundice. As a result of the increased metabolism of the bile pigment, gallstones are quite common, even in children. Generally, the patient's jaundice is of an alcoholuric type; however, occasionally bile is detected in the urine of these patients which may be the result of biliary tract obstruction from gallstones or secondary to hepatic damage from severe hemolytic crises, transfusion induced hepatitis, etc.

Periodic exacerbations of hemolysis can occur and often are related to emotional stress, fatigue, and exposure to cold. During these sudden, relatively minor flare ups, the patient may complain of nausea, vomiting, abdominal pain, and fever. The degree of hemolysis is fairly constant and red cell counts may be normal depending on the compensatory capacity of the marrow. At times, anemia is not found in affected individuals and the diagnosis is established only after another family member has been diagnosed with the disorder.

Fortunately, severe hemolytic crises are infrequently associated with hereditary spherocytosis.[95] Often, these are accompanied by pyrexia, severe dyspnea, vomiting, abdominal pain, tachycardia, and palpitations with occasional fatalities. Their onset is abrupt and generally follows acute infection, frequently of a viral nature. Severe pancytopenia and reticulocytopenia can subsequently develop and marrow evaluation often shows a hypoplastic state during the crisis, particularly affecting the erythroid series. The crisis is augmented by continued shortened red cell survival in non-splenectomized patients, but marrow recovery generally occurs within a few days following such acute episodes. Occasionally, folic acid deficiency can occur related to the increased utilization of folate from rapid red cell turnover. In this situation, reticulocytopenia with pancytopenia may again develop, reflecting the megaloblastic marrow change.

Splenomegaly is expected and those spleens not palpated prior to splenectomy are found to be enlarged at the time of operation. Occasionally hepatomegaly is present, but it is usually not remarkable. Associated abnormalities may include prominent eyes, wide root of the nose, altered teeth, palatal defects, and polydactylia.[27] Typical radiographic abnormalities of chronic anemia may also be present.[16] Chronic, usually bilateral, leg ulcerations unrelated to varicosities represent a rare complication. Interestingly, these ulcerations tend to quickly heal following splenectomy, but their pathogenesis is unclear.[27]

Treatment

Splenectomy is the treatment of choice in hereditary spherocytosis. The response is virtually 100 per cent, with cessation of hemolysis; however, the demonstrable red cell defect persists. Within a few days after splenectomy, red cell survival becomes normal and the intensity of jaundice is reduced.

Hematologists generally agree that an established diagnosis of hereditary spherocytosis warrants splenectomy even when the anemia is fully compensated and the patient is asymptomatic. The longer the hemolytic process persists the greater the potential risks of complications such as aplastic crises and cholelithiasis.

The appropriate timing of splenectomy in the very young has been a much discussed issue. Considerable controversy has existed regarding the incidence of infection following this procedure in children.[11, 15, 47, 50, 51, 75, 119] However, separation into two distinct categories has been helpful in identifying the high risk patients. Normal children who are subjected to splenectomy for ITP, hereditary spherocytosis, or following trauma generally have no significant increased risk of infection postoperatively,[50] while those children with immune deficiency states such as the Wiskott-Aldrich syndrome, malignancy, or other serious underlying diseases have a high incidence of severe and often fatal infections after the procedure.[121]

Splenectomy should be delayed until the third or fourth year of life to help avoid the theoretical risk of increased infection unless severe hemolytic crises or other complications force earlier intervention. The

gallbladder should also be evaluated preoperatively with appropriate x-rays, and at the time of operation. If gallstones are found, cholecystectomy is recommended at the time of splenectomy.

At the time of surgery, a search for accessory spleens should also be made. An overlooked accessory spleen is the most likely cause of failure of response to splenectomy in a correctly diagnosed patient. Splenic implants, "splenosis," occurring within the peritoneal cavity as the result of splenic rupture during splenectomy has been also reported as an occasional cause of relapse in hereditary spherocytosis.

Hereditary Elliptocytosis

Hereditary elliptocytosis or ovalocytosis is a relatively rare autosomal dominant disorder[45] affecting 0.02 to 0.05 per cent of the population. Normally, up to 15 per cent oval or elliptical cells can be seen normally on a peripheral blood smear; in this disorder the incidence is at least 25 per cent, and is commonly as high as 75 to 90 per cent. Elliptocytes also have been seen in higher than normal percentages in sickle cell anemia, thalassemia minor, and hemoglobin-C disease, as well as in macrocytic and hypochromic microcytic anemias.

Of interest is the evidence that in some families the gene connected with this disorder is linked to an Rh blood type, while other families lack such a linkage.[9,24,56,63,89] The hemolytic variant appears to occur more in families *not* shown to possess this Rh linkage. Variability exists as to the degree of hemolysis within the same family. Severe hemolysis most commonly affects those who are felt to be homozygous for this gene.

The cell defect appears to share many features with hereditary spherocytosis—an abnormal cell shape associated with increased splenic destruction and evidence of a membrane permeability defect with resultant increased rate of ATP utilization.[38, 92, 96, 102]

Treatment is splenectomy for all symptomatic patients and cholecystectomy is also to be considered if gallstones are present. After splenectomy, the red cell morphologic defect persists but active hemolysis abates with correction of the anemic state.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

This fascinating disease was initially described in 1925 by Moschcowitz.[90] Subsequently, over 300 cases have been reported and the incidence appears to be increasing, although this may merely reflect better recognition. Classically, thrombotic thrombocytopenic purpura is characterized by a triad consisting of hemolytic anemia of the microangiopathic type, thrombocytopenic purpura, and neurologic abnormalities. Since fever and abnormalities of renal function are also generally present, some prefer to describe a pentad of clinical findings.[81] The classic histopathologic lesion consists of widespread hyaline occlusions (thrombi) affecting small vessels, terminal arterioles, and capillaries.

Clinical Features

The disorder may occur in the newborn or the elderly, but is most common between the ages of 10 and 40, with the peak incidence in the third decade. Two variants are usually seen, an acute and a chronic type. The *acute* form is more common and is fulminating, death frequently occurring within several weeks. The less frequent *chronic* form may be present for months or years. The prodromal phase may include symptoms of arthritis, myalgias, pleuritis, and other vague complaints.

The *anemia* is of a microangiopathic type related to passage of red cells over the damaged small blood vessel walls. It is frequently severe and is the hallmark of this illness. Striking morphologic changes of red cells include characteristic fragmentation, burr cells, and helmet cells present on peripheral smear; secondary marked reticulocytosis and nucleated red cells are also seen. Coombs tests are generally negative, but hyperbilirubinemia of the indirect reacting type is common, often associated with visible jaundice. Hemolysis is the major cause of the anemia, but hemorrhage secondary to thrombocytopenia may also be a contributing factor.

Thrombocytopenic purpura and secondary bleeding manifestations are common. Purpura and retinal hemorrhages occur most frequently, but major gastrointestinal or genitourinary bleeding is also seen.[5] Platelet counts range from 10,000 to 120,000 in most cases. The thrombocytopenia is likely secondary to a shortened platelet life span. Of note are the *usually* normal prothrombin and clotting times, though occasionally they may be prolonged. At times, hypofibrinogenemia is present, suggesting fibrinogen consumption similar to that seen in DIC.

Neurologic manifestations, such as headache, mental change with alterations in the state of consciousness including coma, seizures, paresthesias, aphasia, dysarthrias, visual changes, paresis, and cranial nerve palsies, may be presenting features. These abnormalities are remittent and subject to frequent and rapid alteration. Aphasia and hemiplegia may clear within hours after their appearance, and are secondary to the marked involvement of small vessels in the gray matter of the cerebral hemispheres and brain stem. Cerebral infarction is rarely seen despite the widespread occlusive processes, and this may be responsible for the transiency of neurologic features.[5]

Fever occurs in greater than 90 per cent of the cases sometime during the clinical illness and may be a reflection of a hypothalamic lesion, tissue necrosis, hemolytic products, or pyrogen release from antigen-antibody induced leukocyte damage.[115] Infection has generally not been found.

Renal dysfunction is also frequent, with proteinuria and hematuria, microscopic or gross, occurring in more than 90 per cent of the cases. BUN is initially elevated in greater than 50 per cent of the cases and in higher percentages terminally. Renal dysfunction is not unexpected in light of the frequency of typical renal blood vessel involvement. On occasions, patients may present with acute renal failure secondary to renal cortical necrosis.[46]

Abdominal pain is also a common feature and presumably is related

to microinfarctions of the pancreas and gastrointestinal tract. Serum amylase levels may be elevated, and diabetes has rarely been reported. Other features include hepatomegaly and splenomegaly in 20 to 50 per cent of reported cases, occasional jaundice, and rare heart block secondary to cardiac conduction system infarction.

Confirmation of the clinical impression can be made only by biopsy, showing the histologic evidence of the aforementioned typical lesion. Diagnosis can be made quickly and accurately by bedside biopsy of the readily accessible and highly vascular gingival site.[61] Diagnosis can also be established by histological examination of muscle, skin, bone marrow, lymph nodes, and kidney.

Prognosis and Treatment

Usually associated with a mild onset, this disorder runs a rapidly progressive fatal course. In an extensive review of 271 patients reported by Amorosi and Ultmann,[5] two thirds of the patients with TTP were dead within 3 months of the onset of symptoms. Intracerebral hemorrhage and renal failure are the commonest causes of death.

Reports of remission and recovery have been made with the use of many modes of therapy, including heparin, alone or in conjunction with magnesium therapy; exchange transfusion using fresh blood; fibrinolytic therapy; antimetabolites; massive doses of corticosteroids; dextran; and splenectomy. Since 1966, increasing numbers of clinical remissions have occurred with the combination of high to massive doses of corticosteroids and splenectomy.[65] Goldenfarb and Finch suggest the use of 1000 mg of prednisone daily for 8 to 12 days followed by splenectomy.[61] They point out the usual stabilization of neurologic features and hematocrit values with the high dose steroids prior to surgical intervention. Many of their patients have shown a modest platelet rise during this same period, and most of them generally have not required platelet transfusion during or following splenectomy.

Cuttner[25] suggests initial treatment with splenectomy and reported favorable clinical results in 5 or 6 patients so treated as soon as the diagnosis was confirmed. This procedure was followed postoperatively with high dose corticosteroids (1000 to 1200 mg of Solucortef per day) along with the use of dextran 70. Corticosteroids are continued over several months' time with gradually decreasing doses, and concomitant dextran 70 is continued for 2 weeks. A beneficial effect on the injured vessel wall along with interference of platelet aggregation appears to be the mechanism of dextran action.

The spleen's role in TTP may be similar to hereditary spherocytosis, in which rigid cells are trapped and fragmented. The red cells escaping the splenic circulation may subsequently be even more vulnerable to damage and destruction in the abnormally injured and narrowed peripheral vessels.[112] Thus, splenectomy may interrupt a vicious circle of events and, at times, result in prolonged disease control.

Since the older methods of therapy of this disorder have resulted in less than 10 per cent long-term survivors in more than 300 reported cases, this disease requires quick recognition and treatment. High dose

corticosteroids plus splenectomy, with consideration of dextran therapy, are recommended in light of the more favorable reports of long-term survivors. Unfortunately, the disease continues to be associated with a high percentage of fatalities, and hopefully a better method of treatment will be established after the pathophysiology of this disorder is clarified.

STAGING OF HODGKIN'S DISEASE AND OTHER LYMPHOMAS

In recent years, there has been an increasing trend toward the use of laparotomy for purposes of accurately staging lymphomas, and this section will deal briefly with a discussion of the pros and cons of this procedure in freshly diagnosed cases.

HODGKIN'S DISEASE

Prior to the use of staging laparotomies, the major diagnostic tool in evaluation of the degree of generalized involvement in Hodgkin's disease was the lymphangiogram. Lymphangiography has also been valuable in clarifying the probable mode of spread of Hodgkin's disease. However, a high percentage of lymphangiographic studies proved to be extremely difficult to interpret and were reported as "equivocal" by the radiologist. This finding, associated with the need and value of accurate staging in this disorder, helped bring diagnostic laparotomy into vogue. This procedure has vastly changed our knowledge of the disease and has clearly altered the clinical staging of a significant percentage of patients. This more accurate approach is valuable in predicting the patient's eventual prognosis, in comparing one series with another, and in obtaining guidelines for therapeutic decisions.[57]

This diagnostic staging procedure including splenectomy, open wedge biopsy of the liver, and biopsy of appropriate intra-abdominal nodes has proved to be quite valuable in establishing a more accurate staging of this disorder; many instances of clinically inapparent disease have been detected and frequent areas of clinically suspected disease have been found to be histologically negative. Of interest is the fact that splenic involvement may be the only evidence of subdiaphragmatic disease in a substantial number of cases.

Important observations have resulted from these staging procedures.[57] A small percentage of patients (10 to 15 per cent) were found to have subdiaphragmatic lymph node involvement not detected by lymphography. Splenic hilar nodes were involved in approximately one half of this group and could not be opacified with lower extremity lymphangiogram studies. In addition, a significant number of patients with no splenomegaly, normal liver function studies, and negative lymphangiogram have been found to have occult disease in the spleen or splenic hilar nodes. Determination of splenic involvement has been

notoriously unreliable, with up to 50 per cent of enlarged spleens being negative for tumor; however, spleens over 400 gm are generally all involved. Hepatic involvement has always been found to be associated with splenic involvement. Approximately one third of patients with splenic involvement have hepatic disease and a significant percentage of patients with initial splenic disease will later develop hepatic spread. This suggests spread from the spleen to the liver may be by hematogenous portal dissemination.

Although staging laparotomy has added much to our knowledge of Hodgkin's disease, controversy exists as to whether this approach should be used in *all* freshly diagnosed cases without evidence of disseminated Stage IV disease or limited to those in whom the surgical findings will alter the eventual treatment plan. In this regard, Johnson et al.[70] have pointed out that surgical staging has improved the accuracy of clinical staging, but has not yet been shown sufficiently reliable to withhold prophylactic abdominal radiotherapy on the basis of negative findings. In the review of his patients with Stage I and II disease, he points out that routine laparotomy when viewed retrospectively, added little to therapeutic management. In summary, his experience indicates that laparotomy is not essential in supradiaphragmatic clinical Hodgkin's disease for planning radiation therapy. This assumes an awareness by the radiotherapist for the necessity of prophylactic upper abdominal node and splenic irradiation. In contrast, patients with definite clinical evidence of upper abdominal disease, lumbar node or splenic involvement have an excellent probability of occult lymph node spread to areas outside the usual treatment fields or to the liver. In these patients, he recommends routine abdominal exploration unless a medical contra-indication exists. The likelihood of ineffectual treatment in this group without proper staging is substantial. Splenectomy in those with splenomegaly is also of value in prevention of radiation damage to the left kidney and lung.

Rosenberg[104] states "the major value and utility of exploratory laparotomy and splenectomy is to determine the extent of disease, and then only if the identification of abdominal disease would alter the therapeutic program planned". He points out the major value of this procedure is the providing of better diagnostic information, primarily concerning the spleen, and this is of much value if therapeutic decisions are dependent upon splenic involvement. In essence, he concludes that staging laparotomies should be performed in patients in whom surgical findings may alter the therapeutic approach.[103]

Many argue for routine staging laparotomies on the basis that this procedure frequently changes the clinical stage of the disease and may be critical when open liver biopsy confirms Stage IV disease. Secondly, the surgeon can biopsy nodes not visualized by lymphangiography and get a better overall evaluation by direct exploration of the abdomen. Thirdly, metallic clips or markers can be placed by the surgeon to help the radiotherapist map his field of therapy. Fourthly, the removal of the spleen with placement of a marker at the splenic hilum permits the radiotherapist to better limit his field of radiation and not subject the pa-

tient to possible radiation pneumonitis or nephritis. Fifthly, in females a bilateral oophoropexy may be performed, attaching the ovaries to the posterior uterine wall to hopefully avoid radiation induced sterilization. Finally, some feel tolerance to radiation and chemotherapy is better tolerated after splenectomy. This is a controversial issue without clear data for its support.[110]

The risks of infection following splenectomy has been suggested as a possible deterrent. Most series have failed to show any significant increase in bacterial infection after splenectomy. The incidence of bacterial infection does not seem to be higher in lymphoma patients than in those who undergo splenectomy for other reasons.[43] Goffinet et al.[58] have noted an increase in Herpes zoster infections post-splenectomy which have not interfered with therapy and have not resulted in generalized zoster dissemination.

We generally proceed with staging laparotomies in newly diagnosed cases of Hodgkin's disease and have been impressed with the extremely low morbidity and rare mortality associated with this procedure. The stage of disease, as in other series, has been frequently altered after operation, and we find this of value in our choice of therapy. The most difficult clinical stage is that of a III-B category and presently our approach has been to combine chemotherapy (MOPP) with "curative" radiation therapy. However, each case must be individualized and the optimal approach is one in which the hematologist, surgeon, pathologist, and radiotherapist closely cooperate in the decisions. When the risks of the procedure clearly outweigh its advantages, the laparotomy should be avoided and staging done by non-surgical techniques. It is difficult for one to establish a set rule regarding the best approach to *all* cases of Hodgkin's disease, and flexibility is of great necessity in helping decide the best approach to each patient.

NON-HODGKIN'S LYMPHOMAS

Unlike Hodgkin's disease, the other lymphomas have in the past been considered diseases of multicentric origin and patients with these disorders frequently present with evidence of widespread disease. Recent evidence suggests that these entities often spread in a manner similar to Hodgkin's disease and that staging procedures including laparotomy can be of benefit in determining the extent of involvement and in future treatment planning.

Although the role of staging laparotomy in Hodgkin's disease is clearly established, its role in the non-Hodgkin's diseases is far less certain. The procedure represents the most controversial aspect in staging of these entities. Routine splenectomy was performed at Stanford[71] as part of a pre-treatment evaluation of non-Hodgkin's lymphomas, and Goffinit et al.[59] have analyzed the results. The major staging difference found at laparotomy was the degree of mesenteric node involvement (60 per cent vs. only 2 per cent in Hodgkin's disease).[73] Thus, the procedure's primary usefulness appears to be related to the detection of

disease in the lymph nodes. This is exceedingly important to the radiotherapist as the radiation field must be considerably altered if these nodes are involved. Another important finding was the low probability, less than 20 per cent, of occult abdominal disease when the patient had a negative lymphangiogram and marrow biopsy associated with a non-palpable spleen.

Complications and surgical risks are increased in the non-Hodgkin's lymphomas. This is felt to be related to the older ages of the patients,[57] a more generally debilitated state, and usually more extensive disease. In summary, less is known regarding the value of routine laparotomies with splenectomy in the non-Hodgkin's lymphomas. However, the presence of clinically localized or early disease warrants a consideration of full staging techniques in light of the above information.

MISCELLANEOUS INDICATIONS FOR SPLENECTOMY

Spontaneous Rupture of the Spleen

Spontaneous, or nontraumatic, rupture of the spleen is fortunately an uncommon medical occurrence and may be associated with grave consequences if not quickly recognized and treated. It is commonly a complication of an underlying disease state, although occasionally rupture of a normal spleen has been reported.[14, 93, 94] The multiple diseases which predispose to rupture usually reflect an underlying hematologic or infectious process.[67]

Although rare, spontaneous rupture of the spleen is the commonest cause of death in infectious mononucleosis. Smith and Custer found it second only to malaria as a cause of rupture.[116] The event usually occurs in the second to fourth weeks of the disease when the pathologic changes are most marked.

Diagnosis of rupture naturally depends on the initial recognition of an underlying disease state with the potential for rupture. The acute or insidious onset of left upper quadrant or other abdominal pain often radiating to the left shoulder, is usually the initial symptom. Abdominal pain is uncommon in mononucleosis, for example, and therefore should alert the physician to this underlying possibility. Signs of hypovolemia and shock are frequently seen along with tenderness in the left upper quadrant or flank. A unique clue to diagnosis may be the apparent decrease in splenic size in individuals with hematologic disorders.[111] Shifting dullness secondary to free abdominal blood, nausea, diarrhea, and the urge to defecate may all be present. Laboratory evidence of rupture includes falling hematocrit on serial determination, often associated with leukocytosis. Radiographic examinations show elevation of the left diaphragm, an enlarged splenic shadow and gastric shadow displacement medially. Arteriography may be of value in demonstrating extravasation of the contrast medium into the peritoneal cavity,[10] and abdominal paracentesis is rewarding in approximately half the cases.[78]

The importance of early recognition of this abdominal catastrophe is obvious, so that immediate splenectomy can be performed. Early intervention results in an excellent prognosis.[111]

Wiskott-Aldrich Syndrome and Hereditary Thrombocytopenia

Wiskott-Aldrich syndrome, a sex-linked recessive disease seen in children, is characterized by features of chronic thrombocytopenia, eczema, and immunologic deficiency of both the humoral and cellular immune systems.[13, 22] In contrast to classic idiopathic thrombocytopenic purpura, patients with this syndrome and sex-linked recessive hereditary thrombocytopenia have a near normal platelet survival. Defective platelet production and accelerated catabolism of intrinsically abnormal platelets are considered the more likely causes of thrombocytopenia in these rare states.

Individuals clearly identified as having this disorder have been shown to have a high incidence of infection, often fatal, after splenectomy. Weiden and Blaese[121] suggest that splenectomy in hereditary sex-linked recessive thrombocytopenia may also be associated with an increased risk of serious fatal infection. Some consider this entity to be distinct and separable from the Wiskott-Aldrich syndrome and splenectomy has been reported of therapeutic value in such patients. However, caution is recommended in all such cases because of the potential serious postoperative infectious risks.

Aplastic Anemia

Aplastic anemia is characterized by pancytopenia with associated aplasia or hypoplasia of the bone marrow. The disorder may be idiopathic or secondary to a toxic agent, chloramphenicol and phenylbutazone being common offenders. It continues to be associated with high mortality, and a disease in which medical management is poor. There are scattered reports of the occasional beneficial effects of splenectomy in this disorder.[54, 76, 118] An improved response to platelet transfusion and longer post transfusion platelet survivals in patients who had become refractory to platelet transfusions[54] occasionally are seen. Also, a resultant decreased need for frequency of blood transfusions with higher red cell values has been reported by some along with evidence of partial remission. Obviously, not all patients are candidates for splenectomy in this usually fatal illness. However, it should be considered if the operative risk is reasonable, and if evidence of splenomegaly and/or splenic sequestration of labeled autologous red cells exists.[76] Surprisingly, despite the severe thrombocytopenia and leukopenia in these patients with the high risk of bleeding and infection, surgical complications are rare.[118]

SUMMARY

The purpose of this review has been to present the surgeon with a clearer understanding of these disease states and to allow him to make a more knowledgeable decision regarding the need for splenectomy in their immediate management. The intelligent decision must include a

consideration of the surgical risks in each individual patient, and weighing of the possible beneficial effects from its performance. In general, the operative risk in most patients is low in the hands of an experienced surgeon. We have been impressed with the relatively low incidence of surgical complications and near absent mortality in the large number of our hematologic patients subjected to splenectomy at our institution.[66]

REFERENCES

1. Abramson, N., and Lee, D. P.: Immune Hemolytic Anemias. Disease-A-Month, April 1974, p. 2.
2. Ahn, Y. S.: Vincristine therapy of idiopathic and secondary thrombocytopenias. New Eng. J. Med., *291*:376, 1974.
3. Allgood, J. W., and Chaslin, H., Jr.: Idiopathic acquired autoimmune hemolytic anemia; A review of 47 cases treated from 1955 through 1965. Amer. J. Med., *43*:254, 1967.
4. Altschule, M. D.: A rare type of acute thrombocytopenic purpura, widespread formation of platelet thrombi in capillaries. New Eng. J. Med., 227:447, 1942.
5. Amorosi, E. L., and Ultmann, J. E.: Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine, *45*:139, 1966.
6. Ashby, W.: Determination of length of life of transfusion blood corpuscles in man. J. Exper. Med., 29:267, 1919.
7. Baldini, M.: Idiopathic thrombocytopenic purpura. New Eng. J. Med., 274:1245, 1964.
8. Baldini, M.: Idiopathic thrombocytopenic purpura and the ITP syndrome. Med. Clin. N. Amer., 56:47, 1972.
9. Bannerman, R. M., and Reswick, J. H.: The hereditary elliptocytoses; Clinical and linkage data. Ann. Hum. Genet., 26:23, 1962.
10. Berk, R. N., and Wholey, M. H.: The application of splenic arteriography in the diagnosis of rupture of the spleen. Amer. J. Roentgen., *104*:662, 1968.
11. Bernard, J.: Evolution et trâitement des purpuras thrombopéniques idiopathiques. Acta Haemat., *31*:163, 1964.
12. Best, W. R., and Darling, D. R.: A critical look at the splenectomy-S.L.E. controversy. Med. Clin. N. Amer., *46*:19, 1962.
13. Blaese, R. M., et al.: The Wiskott-Aldrich syndrome: A disorder with a possible defect in antigen processing or recognition. Lancet, *1*:1056, 1968.
14. Blaustein, A.: The Spleen. New York, McGraw-Hill Book Co., 1963.
15. Burman, D.: Congenital spherocytosis in infancy. Arch. Dis. Child., *33*:335, 1958.
16. Caffey, J.: Skeletal changes in chronic hemolytic anemias (erythroblastic anemia, sickle cell anemia and chronic hemolytic icterus). Amer. J. Roentgen., 37:293, 1937.
17. Carbone, P. P., et al.: Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res., *31*:1860, 1971.
18. Carpenter, A. F., et al.: Treatment of idiopathic thrombocytopenic purpura. J.A.M.A., *171*:1911, 1959.
19. Castle, W. B., and Doland, G. A.: Susceptibility of erythrocytes to hypotonic hemolysis as a function of discoidal form. Amer. J. Physiol., *120*:371, 1937.
20. Chauffard, M. A., and Troisier, J.: Anémie grave avec hémolysis ictère hémolysinique dans le serum. Semaine Méd., 28:904, 1908.
21. Coombs, R. R. A., et al.: A new test for the detection of weak and incomplete Rh agglutinins. Brit. J. Exper. Path., 26:255, 1945.
22. Cooper, M. D., et al.: Wiskott-Aldrich syndrome. An immunological deficiency disease involving the afferent limb of immunity. Amer. J. Med., *44*:449, 1968.
23. Crosby, W. H.: Splenectomy in hematologic disorders. New Eng. J. Med., 286:1252, 1972.
24. Cutting, H. O., et al.: Autosomal dominant hemolytic anemia characterized by ovalocytosis. Amer. J. Med., *39*:21, 1965.
25. Cuttner, J.: Splenectomy, steroids, and dextran 70 in thrombotic thrombocytopenic purpura. J.A.M.A., 227:397, 1974.
26. Dacie, J. V.: Autoimmune hemolytic anemias. Brit. Med. J., 2:381, 1970.
27. Dacie, J. V.: The Hemolytic Anemias, Congenital and Acquired, Part I. New York, 2nd ed., Grune and Stratton, 1960.
28. Dacie, J. V.: The Hemolytic Anemias, Congenital and Acquired, Part II. New York, 2nd ed., Grune and Stratton, 1962.
29. Dacie, J. V., and Worlledge, S. M.: Autoimmune hemolytic anemias. Progr. Hematol., 6:82, 1969.

30. Dameshek, W.: Controversy in idiopathic thrombocytopenic purpura. J.A.M.A., *173*:1025, 1960.
31. Dameshek, W., and Miller, E. B.: The megakaryocytes in idiopathic thrombocytopenic purpura, a form of hypersplenism. Blood, *1*:27, 1946.
32. Dameshek, W., and Reeves, W. H.: Exacerbation of lupus erythematosus following splenectomy in "idiopathic" thrombocytopenic purpura and autoimmune hemolytic anemia. Amer. J. Med., *21*:560, 1956.
33. Dameshek, W., and Schwartz, R.: Treatment of certain "autoimmune" diseases with antimetabolites: A preliminary report. J. Assoc. Amer. Physicians, *73*:113, 1960.
34. Dameshek, W., and Schwartz, S. O.: The presence of hemolysis in acute hemolytic anemia; preliminary note. New Eng. J. Med., *218*:75, 1938.
35. Dameshek, W., and Schwartz, S. O.: Hemolysis as the cause of clinical and experimental hemolytic anemias. With particular reference to the nature of spherocytes and increased fragility. Amer. J. Med. Sci., *196*:769, 1938.
36. Dameshek, W., et al.: The treatment of acquired hemolytic anemia with adrenocorticotrophic hormone (ACTH). New Eng. J. Med., *244*:117, 1951.
37. Dameshek, W., et al.: Treatment of idiopathic thrombocytopenic purpura (ITP) with prednisone. J.A.M.A., *166*:1805, 1958.
38. DeGracky, G. C., et al.: Haemolysis and glycolyte metabolism in hereditary elliptocytosis. Brit. J. Haemat., *8*:168, 1962.
39. Desser, R. K., et al.: Staging of Hodgkin's disease and lymphoma: diagnostic procedures including staging laparotomy and splenectomy. Med. Clin. N. Amer., *57*:479, 1973.
40. DeWeese, M. S., and Coller, F. A.: Splenectomy for hematologic disorders. West. J. Surg., Obstet. Gynec., *67*:129, 1959.
41. Doan, C. A.: Hypersplenism. Bull. N. Y. Acad. Med., *25*:625, 1949.
42. Doan, C. A., et al.: Idiopathic and secondary thrombocytopenic purpura: Clinical study and evaluation of 381 cases over a period of 28 years. Ann. Intern. Med., *53*:861, 1960.
43. Donaldson, S. S., et al.: Characterization of post splenectomy bacteremia among patients with and without lymphoma. New Eng. J. Med., *287*:69, 1972.
44. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hemoglobinuria. Münch. Med. Wochenschr., *512*:590, 1904.
45. Dresbach, M.: Elliptical human red corpuscles. Science, *19*:469, 1904.
46. Dunea, G.: Thrombotic thrombocytopenic purpura with acute anemic renal failure. Amer. J. Med., *41*:1000, 1966.
47. Ellis, E. F., and Smith, R. T.: The role of the spleen in immunity: With special reference to the post splenectomy problem in infants. Pediatrics, *37*:111, 1966.
48. Ellis, L. D., and Dameshek, H. L.: Hypersplenism. SURG. CLIN. N. AMER., *55*:277, 1975.
49. Engeset, A., et al.: The thoracic duct lymph in Hodgkin's disease. II. Quantitative analysis of the cellular composition of the lymph. Internat. J. Cancer, *8*:113, 1971.
50. Eraklis, A. J., et al.: Hazard of overwhelming infection after splenectomy in childhood. New Eng. J. Med., *276*:1225, 1967.
51. Erickson, W. D., et al.: The hazard of infection following splenectomy in children. Amer. J. Dis. Child., *116*:1, 1968.
52. Evans, R. S., et al.: Primary thrombocytopenic purpura and acquired hemolytic anemia. Bull. N. Y. Acad. Med., *46*:411, 1970.
53. Fabri, P. J., et al.: A quarter century with splenectomy. Arch. Surg., *108*:569, 1974.
54. Flatow, F. A., and Freireich, E. J.: Effect of splenectomy on the response to platelet transfusion in three patients with aplastic anemia. New Eng. J. Med., *274*:242, 1966.
55. Gall, E. A., and Mallory, T. B.: Malignant lymphoma: A clinicopathologic survey of 618 cases. Amer. J. Path., *18*:381, 1942.
56. Geerdink, R. A., et al.: Hereditary elliptocytosis and hyperhaemolysis: A comparative study of six families with 145 patients. Acta Med. Scand., *179*:715, 1966.
57. Glatstein, E., and Goffinet, D. R.: Staging of Hodgkin's disease and other lymphomas. Ann. Intern. Med., *76*:235, 1972.
58. Goffinet, D. R., et al.: Herpes zoster-varicella infection and lymphomas. Ann. Intern. Med., *76*:235, 1972.
59. Goffinet, D. R., et al.: Staging laparotomies in unselected previously untreated patients with non-Hodgkin's lymphomas. Cancer, *32*:672, 1973.
60. Goldberg, A., et al.: Radiochromium in the selection of patients with hemolytic anemia for splenectomy. Lancet, *1*:109, 1966.
61. Goldenfarb, P. B., and Finch, S. C.: Thrombotic thrombocytopenic purpura: A ten year survey. J.A.M.A., *226*:644, 1973.
62. Gomes, M. M. R., et al.: Indications for splenectomy in hematologic diseases. Surg. Gynec. Obstet., *129*:129, 1969.
63. Goodall, H. B., et al.: Data on linkage in man: Elliptocytosis and blood groups. II. Family 3. Ann. Eugen., *17*:272, 1953.
64. Harrington, W. J., et al.: Demonstration of thrombocytopenic factor in blood of patients with thrombocytopenic purpura. J. Lab. Clin. Med., *38*:1, 1951.

65. Hill, J. B., and Cooper, W. M.: Thrombotic thrombocytopenic purpura: Treatment with corticosteroids and splenectomy. Arch. Intern. Med., *122*:353, 1968.
66. Horsley, B. L., Dameshek, H. L., and Wilde, R. C.: Splenectomy in the adult; an analysis of 200 patients. Unpublished data. University of Pittsburgh School of Medicine.
67. Hyun, B. H., et al.: Spontaneous and pathologic rupture of the spleen. Arch. Surg., *104*:652, 1972.
68. Jacob, H. S., et al.: Abnormal membrane protein of red blood cells in hereditary spherocytosis. J. Clin. Invest., *50*:1800, 1971.
69. Jandl, J. H., and Tomlinson, A. S.: The destruction of red cells by antibodies in man. II. Pyrogenic leukocytic and dermal responses to immune hemolysis. J. Clin. Invest., *37*:1202, 1958.
70. Johnson, R. E., et al.: Results of radiation therapy and implications for the clinical staging of Hodgkin's disease. Cancer Res., *31*:1834, 1971.
71. Jones, S. E., et al.: Non-Hodgkin's lymphomas. III. Preliminary results of radiotherapy and a proposal for new clinical trials. Radiology, *193*:657, 1972.
72. Jones, S. E., et al.: Non-Hodgkin's lymphomas. IV. Clinicopathologic correlation in 405 cases. Cancer, *31*:806, 1973.
73. Kadin, M. E., et al.: Clinicopathologic studies of 117 untreated patients subjected to laparotomy for the staging of Hodgkin's disease. Cancer, 27:1277, 1971.
74. Karpatkin, S.: Autoimmune thrombocytopenic purpura. Amer. J. Med. Sci., *261*:127, 1971.
75. King, H., and Schumacker, H. B., Jr.: Splenic studies; susceptibility to infection after splenectomy performed in infancy. Ann. Surg., *136*:239, 1952.
76. Koch, J. L.: Aplastic anemia and splenectomy. Arch. Intern. Med., *119*:305, 1967.
77. Kuiper, P. J. C., and Livne, A.: Differences in fatty acid composition between normal human erythrocytes and hereditary spherocytosis affected cells. Biochem. Biophys. Acta., 260:755, 1972.
78. Lieberman, R. C., and Welch, C. S.: A study of 248 instances of traumatic rupture of the spleen. Surg. Gynec. Obstet., *127*:961, 1968.
79. LoBuglio, A. F., et al.: Red cells coated with immunoglobulin G; binding and sphering by mononuclear cells in man. Science, *158*:1582, 1967.
80. Lukes, R. J., and Butler, J. J.: The pathology and nomenclature of Hodgkin's disease. Symposium: Obstacles to the Control of Hodgkin's Disease. Cancer Res., 26:1063, 1966.
81. Lukes, R. J., et al.: Thrombotic thrombocytopenic purpura: Clinical and pathologic findings in 49 cases. (Abstr.) Proc. Amer. Soc. Hemat., Montreal, 1960. Blood, *17*:366, 1961.
82. Mayman, D., and Zipursky, A.: Hereditary spherocytosis: The metabolism of erythrocytes in the peripheral blood and in the splenic pulp. Brit. J. Haematol., 27:201, 1974.
83. Meekes, W. R., et al.: Critical evaluation of laparotomy and splenectomy in Hodgkin's disease. Arch. Surg., *105*:222, 1972.
84. Mengel, C., et al.: Hematology, Principles and Practice. Chicago, Year Book Medical Publishers, 1972.
85. Meyers, M. C.: Results of treatment in 71 patients with idiopathic thrombocytopenic purpura. Amer. J. Med. Sci., *242*:295, 1961.
86. Micheli, F.: Ummittelbäre Effekte der Splenektomie bie einem Fall von erworbenen hämolylischen splenomegalischen ikterus, typus Haymen-Widal. Wien. Klin. Wochnschr., 24:1269, 1911.
87. Minkowski, O.: Ueber eine hereditäre, unterdem Bilde eines chronischen Icterus met Urobilinurie, Splenomegalie and Niesensiderosis verlaufende Affection. Verh. Cong. Inn. Med. Wiesbaden, *18*:316, 1900.
88. Mollison, P. L.: Measurement of survival and destruction of red cells in haemolytic syndromes. Brit. Med. Bull., *15*:51, 1959.
89. Morton, N. E.: The detection and estimation of linkage between the genes for elliptocytosis and the Rhesus blood type. Amer. J. Hum. Genet., 8:80, 1956.
90. Moschcowitz, E.: An acute febrile pleiochromic anemia with hyaline thrombosis of terminal arterioles and capillaries; an undescribed disease. A.M.A. Arch. Intern. Med., 36:89, 1925.
91. Motulsky, A. G., et al.: The life span of the elliptocyte: Hereditary elliptocytosis and its relationship to other familial hemolytic diseases. Blood, 9:57, 1954.
92. Murphy, J. R.: Erythrocyte metabolism. VI. Cell shape and the location of cholesterol in the erythrocyte membrane. J. Lab. Clin. Med., 65:756
93. Nicoll, J. A.: Splenic hematoma after spontaneous rupture of the spleen. Amer. J. Surg., *116*:117, 1968.
94. Orloff, M. J., and Peskin, G. W.: Spontaneous rupture of a normal spleen. Internat. Abst. Surg., *106*:1, 1958.
95. Owren, P. A.: Congenital hemolytic jaundice. The pathogenesis of the hemolytic crises. Blood, 3:231, 1948.

96. Peters, J. C., et al.: Erythrocyte sodium transport in hereditary elliptocytosis. Canad. J. Physiol. Pharmacol., *44*:817, 1966.
97. Peters, M. V.: The lymphomas—assessment and treatment. Presented at the Annual Meeting of the Radiological Society of North America.
98. Pirofsky, B.: Autoimmunization and the autoimmune hemolytic anemias. Baltimore, Williams and Wilkins Co., 1969.
99. Rappaport, H.: Tumors of the Hematopoietic System. Atlas of Tumor Pathology, Section III, Fascicle 8. Washington, D.C.: Armed Forces Institute of Pathology, 1966.
100. Rappaport, H.: The clinical and biologic significance of recent observations concerning the spread of Hodgkin's disease. Rev. Franç. d'études Clin. Biol., *14*:449, 1969.
101. Rappaport, H., and Strum, S. B.: Vascular invasion in Hodgkin's disease: Its incidence and relationship to the spread of the disease. Cancer, 25:1034, 1970.
102. Rebuck, J. W., et al.: Electron microscopy of elliptocytes in man and llama. Anat. Rec., *130*:362, 1958. Abstract.
103. Rosenberg, S. A.: A critique of the value of laparotomy and splenectomy in evaluation of patients with Hodgkin's disease. Cancer Res., *31*:1737, 1971.
104. Rosenberg, S. A.: Annotation: Splenectomy in the management of Hodgkin's disease. Brit. J. Haemat., 23:271, 1972.
105. Rosenberg, S. A., and Kaplan, H. S.: Evidence for an orderly progression in the spread of Hodgkin's disease. Cancer Res., 26:1225, 1966.
106. Rosenberg, S. A., and Kaplan, H. S.: The results of radical radiotherapy in Hodgkin's disease and other lymphomas. *In* Zarafonetis, C., ed.: Proceeding of the International Conference on Leukemia-Lymphoma, Philadelphia, Lea and Febiger, 1968, p.403.
107. Rosenberg, S. A., et al.: Report on the Committee on Hodgkin's Disease Staging Procedures. Cancer Res., *31*:1862, 1971.
108. Rosse, W.: Quantitative immunology of immune hemolytic anemia II. The relationship of cell bound antibody to hemolysis and the effect of treatment. J. Clin. Invest., 50:734, 1971.
109. Rosse, W. F., and Logue, G. L.: Immune hemolytic anemias. Mod. Treat., *8*:379, 1971.
110. Salzman, J. R., and Kaplan, H. S.: Effect of splenectomy on hematological tolerance during total lymphoid radiotherapy of patients with Hodgkin's disease. Cancer, 27:471, 1971.
111. Schwartz, S. I., et al.: Splenectomy for hematologic disorders. Arch. Surg., *101*:338, 1970.
112. Schwartz, S. I.: Splenectomy for hematologic disorders. Current Problems in Surgery, May 1971.
113. Shulman, N. R., et al.: Similarities between known antiplatelet antibodies and the factor responsible for thrombocytopenia in idiopathic purpura. Physiologic, serologic and isotopic studies. Ann. N. Y. Acad. Sci., *124*:499, 1965.
114. Sloane, G. L., et al.: Splenectomy in hematologic disorders. Amer. J. Surg., *104*:94, 1962.
115. Snell, E. S., et al.: Properties of human endogenous pyrogen. Clin. Sci., *16*:615, 1957.
116. Smith, E. B., and Custer, R. R.: Rupture of the spleen in infectious mononucleosis: A clinicopathologic report of 7 cases. Blood, *1*:317, 1946.
117. Umlas, J., and Kaiser, J.: Thrombohemolytic thrombocytopenic purpura. (TTP). A disease or a syndrome? Amer. J. Med., *49*:723, 1970.
118. Vincent, P. C., and DeGrucky, G. C.: Complications and treatment of aplastic anemia. Brit. J. Haemat., *13*:977, 1967.
119. Walter, L. E., and Chaffin, L.: Splenectomy in infants and children. Ann. Surg., *142*:798, 1965.
120. Weed, R. I.: New thought on hereditary spherocytosis. Med. Coll. Virginia Quart., 6(2):50, 1970.
121. Weiden, P. L., and Blaese, M.: Hereditary thrombocytopenia: Relation to Wiskott-Aldrich syndrome with special reference to splenectomy. J. Pediat., *80*:226, 1972.
122. Welch, C. S., and Dameshek, W.: Splenectomy in blood dyscrasias. New Eng. J. Med., 242:601, 1950.
123. Widal, F., et al.: Autoagglutination des hématies dans l'ictere hemolytique. C. R. Soc. Biol. (Paris), *64*:655, 1908.
124. Wilde, R. C., et al.: Splenectomy for chronic idiopathic thrombocytopenic purpura. Arch. Surg., 95:344, 1967.
125. Williams, W. J., et al.: Hematology. New York, McGraw-Hill, 1972.
126. Wintrobe, M. M.: Clinical Hematology. Philadelphia, Lea and Febiger, 6th ed., 1967.
127. Young, J. M.: The thoracic duct in malignant disease. Amer. J. Path., 32:253, 1958.
128. Young, L. E.: Observations on inheritance and heterogeneity of chronic spherocytosis. Trans. Assoc. Amer. Physicians, *68*:141, 1955.

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The Dilemma of Hypersplenism

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The dilemma of hypersplenism has perplexed clinicians since the clinical syndrome was first recognized in 1866 by Gretsel as "splenic anemia."[11] Confusion and controversy have continued for over a century regarding definition of the syndrome, its pathogenesis and etiology, and indications for splenectomy. Jandl and Aster[6] in 1967 stated that no expression in medicine is used by so many to describe such variegated phenomena as hypersplenism. Although there continue to be missing links in our understanding of the syndrome, increasing unanimity among hematologists and surgeons has grown with respect to the indications for and merits of splenectomy in this syndrome.

Three essential features which characterize the syndrome of hypersplenism: (1) Splenomegaly. (2) Cytopenia(s) associated with hyperplasia of bone marrow. The reduction in circulating blood cells may involve red blood cells, granulocytes, and platelets either singly or in any combination. (3) Correction of the cytopenia(s) by splenectomy—the "sine qua non" of the diagnosis of this syndrome.

While the dilemma regarding pathogenesis has remained unresolved for over a century, two views include: sequestration of blood cells which is enhanced by the enlarged spleen, and production by the spleen of a humoral substance which inhibits the production or release of blood cells by the bone marrow. There is increasing evidence that sequestration is primarily responsible for this syndrome, primarily from two studies. First, significant decreases in granulocyte and platelet counts can be demonstrated across the splenic circulation by sampling arterial and venous blood.[11] Second, red blood cells or platelets tagged with chromium-51 and injected into patients with hypersplenism results in increased radioactivity over the enlarged spleen.[11] If this increased radioactivity, reflecting sequestration, has a greater than 2:1 ratio when compared with similar monitoring of the liver, it is more likely that splenectomy will be of therapeutic value.

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Evidence supporting the "humoral" theory is less convincing. There is no question, however, that some patients with aplastic or hypoplastic anemias occasionally respond to splenectomy. In addition, a significant number of patients with typical hypersplenism do not respond to splenectomy in spite of positive radioactive sequestration studies, suggesting that sequestration is not the only pathogenetic mechanism.

ETIOLOGY

Hypersplenism is either a primary or idiopathic hematologic disorder or it is a syndrome induced by splenomegaly produced by a variety of diseases. The latter is referred to as secondary hypersplenism.

Primary Hypersplenism

This interesting syndrome formerly was termed splenic neutropenia. It has been recognized more frequently in recent years and is not confined to a cytopenia of only the white blood cells. On a clinical level the diagnosis is one of exclusion after a careful search for a cause of the hypersplenism has been unrewarding, and the pathology of the removed spleen is not diagnostic of any secondary underlying disease. Table 1 lists the criteria for the diagnosis of this specific hematologic syndrome.

Dacie et al.[3] refer to this syndrome as "nontropical idiopathic splenomegaly" and have emphasized the value and safety of splenectomy in alleviating the cytopenia and abdominal discomfort from the splenomegaly. These authors also reported that 2 of their series of 10 patients who underwent splenectomy subsequently developed lymphosarcoma. This experience is in agreement with our own as well as that of others.[1, 7] We followed 6 of 12 patients who fulfilled the criteria for the diagnosis of primary hypersplenism for 10 years. Three of the 6 patients developed chronic lymphatic leukemia or lymphosarcoma within 18 months of splenectomy. Others have reported a significant occurrence of acute leukemia in these patients after splenectomy.[1, 7]

It seems appropriate to consider primary hypersplenism as a relatively specific hematologic syndrome which responds favorably to splenectomy and then follows either a benign or a malignant course. In some patients it represents a pre-lymphoma or pre-leukemia state, which is recognized only when the malignancy develops at a point in time after the splenectomy.

Table 1. *Criteria for Diagnosis of Primary Hypersplenism*

1. Criteria for hypersplenism present (splenomegaly, cytopenia, hyperplastic marrow)
2. No secondary etiology discovered clinically
3. Pathology of spleen nondiagnostic
4. Good response to splenectomy
5. Possible lymphoma or leukemia after splenectomy

Table 2. *Causes of Secondary Hypersplenism*

Primary liver disease
Cirrhosis (Laennec's and postnecrotic)
Chronic hepatitis
Wilson's disease
Schistosomiaisis
Extrahepatic portal or splenic vein obstruction
Collagen-vascular disease
Systemic lupus erythematosus
Felty's syndrome
Hematologic diseases
Non-Hodgkin's lymphomas
Hodgkin's disease
Acute and chronic leukemias
Idiopathic myelofibrosis
Polycythemia vera
Congenital hemolytic anemias (hemoglobinopathies, spherocytosis, P-K deficiency)
Infections
Acute (infectious mononucleosis, SBE, psittacosis)
Chronic (miliary tuberculosis, malaria, brucellosis, Kala-azar, syphilis, histoplasmosis)
Miscellaneous infiltrative diseases of the spleen
Sarcoidosis
Reticuloendothelioses (Gaucher's disease)
Amyloidosis

Secondary Hypersplenism

The possible causes of secondary hypersplenism are multiple and diverse (Table 2). It is essential, however, that all possible causes be entertained both before and after splenectomy in order that appropriate treatment of the primary disease can be administered. A recommended clinical diagnostic approach to the patient who has the established diagnosis of the syndrome of hypersplenism is included in Table 3. Approximately 50 per cent of patients in whom the diagnosis of the primary disease is unknown at the time of the appearance of hypersplenism will be discovered to have a specific disease with this type of complete clinical evaluation. Another 10 per cent will require examination of sections of the spleen, liver, or lymph nodes obtained at the time of splenectomy to establish the cause of the hypersplenism. The remaining patients will fall into the previously discussed category of "primary hypersplenism."

THERAPY

After the diagnosis of hypersplenism is established the therapeutic dilemma of splenectomy versus treatment of underlying disease and ob-

Table 3. *Clinical Evaluation of Hypersplenism*

1. Careful history and physical and routine laboratory studies
2. Skin tests for tuberculosis, histoplasmosis, etc.
3. Serologic tests for collagen diseases
4. Immunoprotein studies
5. Needle biopsy of liver and culture
6. Bone marrow biopsy and culture
7. Lymph node biopsy and culture (if adenopathy present)
8. Angiography of hepatic and splenic circulation

servation of the hematologic picture must be resolved.

In primary hypersplenism there is general agreement that splenectomy is indicated once the diagnosis is made on clinical grounds. Not only will the surgical removal of the spleen usually result in improvement, but it also may provide a specific diagnosis when the spleen sections are examined carefully by the pathologist.

When there is a known cause for the hypersplenism (secondary) the indications for splenectomy are not as clear. The severity and prognosis of the primary disease process must be carefully evaluated and the risk of surgery weighed against the benefit achieved by relieving the hypersplenic state. There is an increasing tendency among hematologists to recommend splenectomy earlier in many of the diseases associated with hypersplenism even if one can expect only a decrease in transfusion requirements, decrease in number of infections, prevention of some hemorrhagic phenomena, or palliation of pain. Since the decision to proceed with splenectomy depends greatly upon the primary disease responsible for the splenomegaly, a discussion of each major disease category seems warranted.

PRIMARY LIVER DISEASE

By far the most common cause of secondary hypersplenism in any hospital is primary liver disease. Laennec's or alcoholic cirrhosis and post-necrotic or post-hepatic cirrhosis are the liver diseases most often responsible for the development of secondary hypersplenism. The splenomegaly associated with these chronic liver diseases is clearly secondary to chronic splenic vein hypertension, which is usually associated with portal vein hypertension as well.

When the syndrome of hypersplenism occurs in these patients it may be an isolated manifestation of splenic vein hypertension without the serious consequences associated with portal hypertension (e.g., esophageal and gastric varices and ascites). In these patients the indications for splenectomy would be the same as those for any patient with secondary hypersplenism (Table 4). However, when the clinical manifestations of portal hypertension are also present to a degree necessitating a portal-systemic-venous shunt operation, the indications for splenectomy as an additional surgical procedure are more difficult to establish. If the patient has a cytopenia(s) which is causing clinical dif-

Table 4. *Indications for Splenectomy in Hypersplenism*

1. Primary Hypersplenism—Once diagnosis is established
2. Secondary Hypersplenism
   a. Dependent upon primary disease, medical status of patient, and prognosis
   b. Early splenectomy indicated in non-Hodgkin's lymphomas
   c. Common causes of secondary hypersplenism when following present:
      (1) Major hemolysis with symptomatic anemia and transfusion requirement
      (2) Neutropenia of marked degree (< 1000 polymorphs per cu mm) with recurrent infections
      (3) Thrombocytopenia causing purpura or hemorrhage
      (4) Massive splenomegaly causing incapacitating symptoms

ficulties, splenectomy should be considered either at the time of the shunt procedure or as an independent operation before or after the shunt, depending upon the overall clinical status and the urgency for the shunt.

For example, if a patient with marked neutropenia (<1000 granulocytes per cu mm) secondary to hyersplenism also has had several hemorrhages from esophageal varices, the morbidity of the portocaval shunt may be reduced considerably by performing splenectomy first in order to alleviate the granulocytopenia and thus avoiding the risk of serious postoperative infection following the shunt procedure. Similarly, a significant thrombocytopenia clearly due to hypersplenism (platelet count < 40,000 per cu mm) would be an indication for splenectomy prior to the shunt in order to prevent major operative and postoperative bleeding.

If technically feasible and if the patient's general condition permits, combining splenectomy with a splenorenal shunt is ideal for patients with significant problems associated with both splenic and portal venous hypertension.

A portocaval shunt alone may transiently or partially relieve splenic venous hypertension and its resultant congestive splenomegaly and thus favorably affect the hypersplenism. However, improvement in the cytopenias, if it occurs, is usually quite transient.

In summary, splenectomy is indicated in patients with secondary hypersplenism of clinical significance due to cirrhosis of the liver. If there is associated portal hypertension of a degree requiring a venous shunt operation, the hypersplenism should then be treated by splenectomy first, in order to reduce the morbidity and mortality of the longer and more potentially serious portal-systemic venous shunt. If feasible, splenectomy and splenorenal shunt is an ideal operation for these patients.

COLLAGEN-VASCULAR DISEASE

Hypersplenism with resultant cytopenias may occur in systemic lupus erythematosus or in Felty's syndrome. In these disorders, there is also the possibility that the cytopenia may have an autoimmune basis and therefore may be favorably treated with steroids. The indications for

splenectomy in these patients should be quite strict since one must carefully assess the patient's overall clinical status as well as his prognosis. For example, if the patient with systemic lupus erythematosus or Felty's syndrome has not had any infections, bleeding episodes, or symptoms from anemia, splenectomy for hypersplenism should not be performed. However, splenectomy is indicated for patients with significant neutropenia associated with recurrent infections, thrombocytopenic purpura, or symptomatic anemia requiring transfusions if it is determined the patient can tolerate surgery.

HEMATOLOGIC DISEASES

Malignant Lymphomas

Hypersplenism with resultant cytopenia(s) occurs not uncommonly both in the non-Hodgkin's lymphomas and in Hodgkin's disease.

Recent reports by O'Brien et al.[8] and Yam and Crosby[12] have demonstrated the value of early splenectomy in hypersplenism in the non-Hodgkin's lymphomas, particularly the well-differentiated lymphocytic varieties (lymphosarcoma, chronic lymphocytic leukemia, and giant follicular lymphomas). Yam and Crosby emphasize the importance of early splenectomy once hypersplenism, however mild, develops in these lymphoproliferative disorders. Thirty-nine of their series of 50 patients had favorable responses to splenectomy. In 27 of these 39, responses lasted more than 6 months. Postoperative complications were infrequent. The effect of splenectomy on survival could not be determined because of lack of a control study. However, 6 patients were alive and well 5 years after splenectomy. Apparent curability of a group of patients with giant follicle lymphomas of the spleen has been emphasized by Hickling.[4] In the current classification of the non-Hodgkin's lymphomas, the patients reported by Hickling fit the category of well-differentiated, nodular, lymphocytic non-Hodgkin's lymphomas.

A specific type of non-Hodgkin's lymphomas termed leukemic reticuloendotheliosis or "hairy cell disease" has a most favorable response to splenectomy for early manifestations of hypersplenism. In fact, splenectomy is the only treatment recommended for this disorder.

In contrast to the non-Hodgkin's lymphomas, hypersplenism occurs late in Hodgkin's disease when stage III-B or IV of the disease is present. The results of splenectomy have been poor and the morbidity and mortality quite high.[8, 10]

Leukemias

Except for the chronic lymphocytic leukemia which is best considered with the non-Hodgkin's lymphomas, indications for splenectomy for hypersplenism in leukemia are few. In the acute leukemias, the morbidity and mortality are prohibitive, with little hope for any significant response. In chronic myelocytic leukemia the spleen may become huge with associated symptoms of pain and discomfort. Some degree of hypersplenism may develop but may be difficult to interpret, particularly

if there is incipient or actual blast crisis. Splenectomy for chronic myelocytic leukemia is therefore rarely, if ever, indicated because of the poor prognosis and morbidity and mortality of the procedure.

Idiopathic Myelofibrosis with Myeloid Metaplasia

Agnogenic myeloid metaplasia is usually associated with myelofibrosis, massive splenomegaly, and a leukoerythroblastic peripheral blood smear. A small group of patients with myeloid metaplasia have a cellular marrow.

Hypersplenism, massive symptomatic splenomegaly, splenic infarctions, a terminal "blast crisis" plus portal hypertension are the major complications of this disorder. Hypersplenism is usually manifested by significant hemolytic anemia or severe thrombocytopenic purpura. The resultant cytopenias are especially severe because of the associated impaired blood cell production due to the myelofibrosis.

Splenectomy for hypersplenism in this disorder has been associated with a high morbidity and mortality in the past.[10] Recent series,[11] especially the Mayo experience, have demonstrated an acceptable morbidity and mortality from splenectomy when the indications are restricted. Silverstein and Remine[11] believe the procedure is indicated in those patients who have: (1) major hemolysis not relieved by medical management, (2) life-threatening thrombocytopenia, (3) progressive and massive splenomegaly leading to severe incapacitating discomfort, or (4) portal hypertension. Their results in 29 patients who underwent splenectomy demonstrated 3 immediate postoperative deaths and 11 serious postoperative complications. However, those who survived the procedure also survived longer than those treated medically for major hemolysis and massive splenomegaly. These authors emphasized an apparent advantage for females in terms of postoperative complications and survival.

The indications for splenectomy in this serious myeloproliferative disorder must be rigid and individualized because of the persistent high morbidity and mortality.

Polycythemia Vera

It is a rare patient with polycythemia vera who manifests hypersplenism. When it occurs, there most likely has been a transformation of the myeloproliferative syndrome to myelofibrosis with myeloid metaplasia and the preceding remarks are applicable.

Congenital Hemolytic Anemias

Although hypersplenism per se is not the basic or primary reason for hemolysis in the hemoglobinopathies, thalassemias, or congenital nonspherocytic hemolytic anemias, it may play a contributory role as the splenomegaly becomes progressive.

Congenital spherocytic hemolytic anemia (hereditary spherocytosis) is a unique example of a specific hypersplenic syndrome in which splenectomy is curable 100 per cent of the time.

Increased sequestration in the spleen should be demonstrated by investigative studies prior to considering splenectomy for improving the anemia in all of the congenital hemolytic anemias. In most instances, the transfusion requirement may be decreased and the anemia only partially improved even when splenectomy is successful.

Infections

Hypersplenism may occur with a variety of acute and chronic infections, some of which are listed in Table 2. Usually, appropriate antimicrobial treatment of the primary infectious disease alleviates the splenomegaly and therefore the hypersplenism is relieved.

It is possible in some instances, especially with chronic granulomatous infections, that the splenomegaly and resultant hypersplenism will persist after the completion of an adequate course of antibiotics. If this occurs, splenectomy is indicated. We have seen two patients in this category with subacute bacterial endocarditis. They both had persistent splenomegaly with a significant cytopenia long after adequate courses of intravenous antibiotic therapy. Splenectomy was curative in both cases.

Infiltrative Diseases of the Spleen

Many disorders of varying etiology may produce splenomegaly and hypersplenism as a result of infiltration and replacement of splenic tissue. In these diseases, splenectomy is indicated for palliation if the hypersplenism is significant and more threatening to life than the primary disease itself.

SUMMARY

While the dilemma of hypersplenism has not yet been resolved, we do have a clearer understanding of the pathogenesis of this syndrome. Once hypersplenism is established in a patient, the indications for splenectomy are dependent upon the primary disease process and the associated prognosis. There is an increasing tendency for early splenectomy in primary hypersplenism and in secondary hypersplenism associated with the non-Hodgkin's lymphomas of the well-differentiated lymphocytic variety.

Each patient with the syndrome of hypersplenism must be evaluated individually and the decision for splenectomy made only after careful hematologic and medical investigation and an informed dialogue between the surgeon and the hematologist.

REFERENCES

1. Block, M., Jacobson, L. O., and Bethard, W. F.: Preleukemic acute human leukemia. J.A.M.A., *152*:1018, 1953.
2. Dacie, J. V., et al.: Non-tropical idiopathic splenomegaly (primary hypersplenism): A review of ten cases and their relationship to malignant lymphomas. Brit. J. Haemat., *17*:317, 1969.

3. Dameshek, W.: The spleen; facts and fancies. Bull. New Eng. Med. Cent., 3:304, 1941.
4. Hickling, R. A.: Giant follicle lymphoma of the spleen. Brit. Med. J., 2:787, 1964.
5. Jandl, J. H., and Aster, R. H.: Increased splenic pooling and the pathogenesis of hypersplenism. Amer. J. Med. Sci., 253:383, 1967.
6. Meacham, G. C., and Weisberger, A. S.: Early atypical manifestations of leukemia. Ann. Intern. Med., *41*:780, 1954.
7. O'Brien, P. H., Hartz, W. H., Derlack, D., et al.: Splenectomy for hypersplenism in malignant lymphoma. Arch. Surg., *101*:348, 1970.
8. Schultz, J. C., Denny, W. F., and Ross, S. W.: Splenectomy in leukemia and lymphoma: Report of 24 cases. Amer. J. Med. Sci., 247:64130, 1964.
9. Schwartz, S. I., et al.: Splenectomy for hematologic disorders. Arch. Surg., *101*:338, 1970.
10. Silverstein, M. N., and Remine, W. H.: Sex, splenectomy, and myeloid metaplasia. J.A.M.A., 27:424, 1974.
11. Williams, W. J., et al.: Hematology. New York, McGraw-Hill Book Co., 1972.
12. Yam, L. T., and Crosby, W. H.: Early splenectomy in lymphoproliferative disorders. Arch. Intern. Med., *133*:270, 1974.

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Surgery of the Spleen

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For 2,000 years the surgical aspects of splenic disease have been surrounded by an aura of mystique. Galen described the spleen as an organ full of mystery.[1] Pliny thought the spleen produced mirth, and persons with large spleens were thought to laugh excessively.[17] Morgagni's observation in 1680 that removal of the spleen did not impair health added to the mystique.[17]

Splenectomy allegedly was first practiced by the ancients in the belief that it improved the speed of runners. An old English translation of Pliny[19] describes this belief.

> "The member (the spleen) hath a propriete by itself sometimes to hinder a man's running; whereupon professed runners in the race thath are troubled with the splene, have a devise to burn waste it with a hot yron."

The first recorded splenectomy in a human being was done by Zaccarelli of Naples in 1849.[19] The operation was performed for splenomegaly and the patient, a 24 year old woman, is said to have been cured in 24 days. The veracity of this report has been questioned by many historians. There are two other reports of splenectomy in the sixteenth century and two cases in the seventeenth century, all quite scanty.[19] These early successful extirpations were carried out for penetrating abdominal trauma and consisted of removal of the damaged spleen from the open wound. In America successful splenectomy was first reported by O'Brien in 1816 for splenic prolapse following a knife wound.[18]

By the middle of the eighteenth century the way was paved for the deliberate extirpation of the spleen. Laboratory experiments by Zambeccari, Malpighi, and Clarke[19] had shown that in animals the spleen was not necessary for life. The normal survival of patients who had splenectomy for trauma confirmed these animal findings.

In 1826 Karl Quittenbaum planned the first splenectomy for primary splenic disease, but the patient survived for only 6 hours after operation.[20] In 1866 Spencer Wells performed the first elective splenectomy in England.[27] Collier published a review of 29 cases of splenec-

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tomy in 1882 and pointed out that splenectomy in leukemia was not uniformly fatal.[5]

Unfortunately, cirrhosis of the liver and leukemia were among the diseases of the spleen first surgically treated. A high mortality rate resulted as was reported by Johnston in 1908 with 66 deaths in 355 cases (19 per cent).[12] Surgical technique improved and an increased understanding of hematologic disorders also occurred. The scope of surgical correction of splenic disease broadened and was refined. Understanding of the role of the spleen in congenital and acquired hemolytic diseases such as congenital spherocytosis and idiopathic thrombocytopenic purpura led to the first splenectomy for purpura by Kaznelson in 1923.[11]

In 1928 Mayo reported the first large series of patients who had splenectomy (500 cases), and demonstrated a good and sometimes prolonged remission in leukemia and lymphoma.[15] The function of the spleen as a filter and as a reticuloendothelial organ have been well elucidated during the past 40 years. The role of the spleen in immune mechanisms is the remaining mystery of splenic function. Even though the frequency of splenectomy for hematologic disorders has increased during the past decade, there remains in many instances uncertainty as to the value of the procedure.

The results of splenectomy in hematologic disease depend largely on teamwork and the selection of cases by the hematologist. As Whitley has stated, the hematologist is the arbiter and the dictator of the surgery of the spleen. "Save for rupture of the organ, it is not often that a spleen is removed without the hematologist having, not a finger in the pie, but a needle in a vein, the sternum, or the spleen itself."[33]

Over the years, there have been significant changes in the indications for splenectomy. Initially, injury to the organ constituted the most common indication for operation. During the 1950's and 1960's advances in hematology led to operations for hypersplenism or other hematologic abnormalities. Now, as Fabri has reported, as many as 29 per cent of the splenectomies performed are incidental. The increasing frequency with which surgeons must perform splenectomy mandates a thorough knowledge of splenic anatomy and the surgical technique of splenectomy. The indications for splenectomy are discussed in detail elsewhere in this symposium and will not be reviewed here.

SURGICAL ANATOMY

The normal spleen, a specialized capillary bed, weighs 180 gm, is 12 cm in length, and is located high in the left upper quadrant of the abdomen. Its position is maintained by two folds of peritoneum which form the avascular phrenicolienal and gastrolienal ligaments. The lower pole is supported by the liencolic ligament. The normal sized spleen is not palpable as it lies beneath the diaphragm at the level of the ninth, tenth, and eleventh ribs (Fig. 1). The splenic artery arises from the celiac axis and follows a tortuous course behind the pancreas, yielding the short gastric arteries to the greater curvature of the stomach before

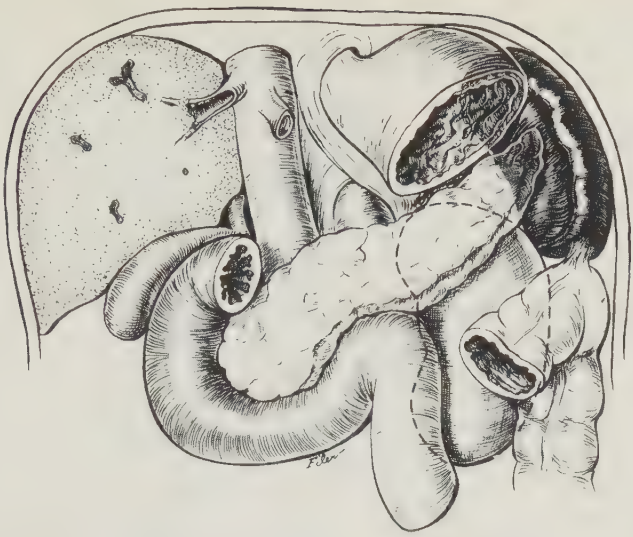

Figure 1. *Anatomic Relationships of the Spleen.* The spleen is supported high in the left upper quadrant in close apposition to the stomach, tail of the pancreas and transverse colon.

it divides within the splenic hilum. The splenic vein returns blood from the spleen to the portal circulation. Five or six branches from the splenic parenchyma unite to form a single vessel which passes left to right, grooving the upper and back part of the pancreas, below the splenic artery. Behind the neck of the pancreas the vein unites at a right angle with the superior mesenteric vein to form the portal vein. The splenic vein receives the short gastric veins, the pancreatic veins, and the inferior mesenteric veins.

The capsule of the human spleen is 1 to 2 mm thick but can become considerably thicker both in primary splenic disease and in certain inflammatory diseases of the abdomen. Blood vessels enter the splenic substance and follow connective tissue trabeculae dividing the spleen into progressively smaller compartments. The spleen's complex microcirculation and its relation to reticuloendothelial cells provide the matrix for the filtering and sequestering function of the spleen.

PHYSICAL AND X-RAY EXAMINATION OF THE SPLEEN

Physical examination plays an important role in the evaluation of patients with surgical diseases of the spleen, but examination of the spleen is not a simple procedure to accomplish. The spleen must be one third enlarged before transabdominal palpation is possible. Percussion dullness along the medial aspect of the tenth and eleventh ribs may indicate splenic enlargement before it becomes detectable by palpation. Bimanual palpation of the spleen is carried out by placing the left hand

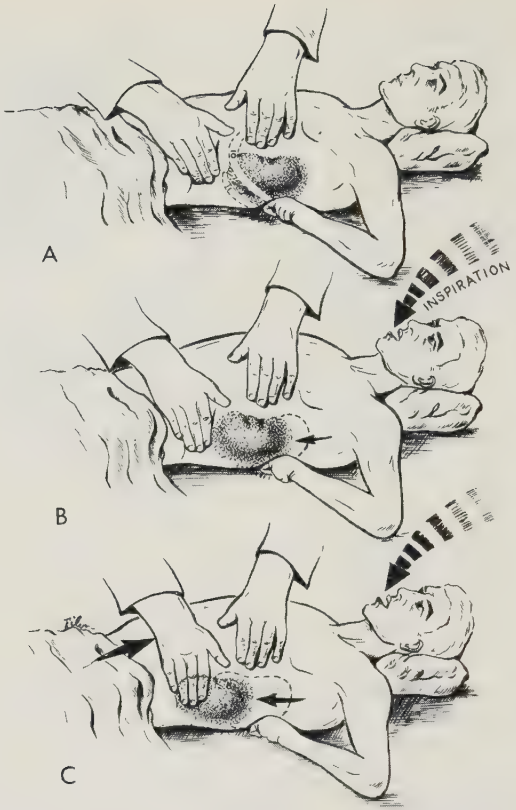

Figure 2. *Method of Examination of the Spleen. a,* The right hand is placed on the abdominal wall. *b,* As the diaphragm descends with inspiration, the spleen moves caudally. *c,* The right hand rides over the inferior margin of the spleen at the peak of inspiration.

over the lateral aspect of the costal margin and exerting compression, leaving a loose fold of skin over the costal margin. The right hand lies on the abdominal wall just below the margin of the ribs. The hands are kept still and just before the peak of inspiration the hands are drawn together with the right hand dipping beneath the costal margin. If the spleen is palpable the finger tips will ride momentarily over its edge. An enlarged spleen moves freely with respiration and has a sharp anterior edge which may be notched at the splenic hilum (Fig. 2).

Visceral pain observed in splenic disorders is secondary to splenic enlargement and capsular distention. Such pain is felt directly over the spleen and is associated with tenderness of the enlarged, tense organ. A second form of pain is secondary to compression of surrounding soft tissue structures and is perceived as local somatic pain transmitted by the corresponding intercostal nerves. A third form of pain is phrenic or diaphragmatic pain felt at the tip of the shoulder. The embryologic diaphragm develops in the region of the fourth cervical segment, and nerve fibers from C3, C4, and C5 descend with the diaphragm during sub-

sequent maturation. Irritation of the diaphragm by the enlarged spleen or a splenic hematoma yields pain in the left supraclavicular space and over the left acromion process of the scapula or over the lateral aspect of the clavicle. Sometimes the tenderness can be elicited by compression of the left phrenic nerve in the neck (Seagesser's sign). Shoulder pain is most frequently observed in splenic rupture with hematoma formation.

X-ray detection of splenomegaly is most often accomplished by plain roentgenography. An enlarged spleen is easily visualized and measured. The spleen is regarded as enlarged if the length exceeds 14 cm and the width is greater than 8 cm. The left hemidiaphragm may be elevated when the spleen is massive. The stomach contour is changed in about 70 per cent of patients with splenic enlargement.[21] The greater curvature of the stomach becomes arch-shaped and is compressed toward the midline. The antrum is also medially displaced and flattened. Occasionally, the splenic flexure of the colon is depressed and an impression on the colon is made by the lower pole of the spleen. In splenic rupture, gastric dilatation and prominent gastric mucosal folds are often observed, probably secondary to irritation caused by a hematoma in the gastrosplenic ligament. In such cases, the splenic flexure of the colon is often distended, representing a form of localized ileus in response to the injury.

Abdominal angiography has become an important diagnostic procedure in the evaluation of occult splenomegaly or an obscure left upper quadrant mass or unrecognized splenic injury. Selective catheterization and injection of the celiac axis identifies such uncommon entities as splenic artery aneurysm, splenic cyst, and benign or metastatic tumors of the spleen. Venous phase angiography and splenoportography outline the portal venous system and are essential in the evaluation of portal hypertension and esophageal varices.

Radioisotopic scans are valuable in recognition of occult splenomegaly, in identifying the nature of a left upper quadrant mass, for detection of space occupying lesions within the spleen, and for identifying accessory spleens. Multiple views provide good structural detail of the spleen. The principal role of the spleen scan is detection of splenomegaly that is not apparent by physical or conventional radiologic examination.

SPLENECTOMY

Preoperative Preparation

Preoperative preparation of patients who will undergo elective splenectomy plays a large role in determining a successful uncomplicated postoperative course. The coagulation status of the patient must be studied and abnormalities corrected if possible. In cases of thrombocytopenia, platelets are not usually administered prior to ligation of the splenic artery, but their need should be anticipated. Platelet donor packs should be available prior to initiation of the operation. Similarly, fresh frozen plasma may be necessary in patients who have a deficit of

hepatic coagulation factors. Abnormalities of the prothrombin time are corrected prior to operation by the administration of vitamin K. Significantly anemic patients should receive transfusions of packed red cells or fresh whole blood prior to operation. Adequate oxygen-carrying capacity is usually achieved with a hematocrit between 25 and 30 per cent.

Specific infections should be vigorously treated with culture-specific antibiotics, especially in patients whose resistance has been affected by administration of immunosuppressive agents. Prophylactic antibiotics are not indicated in patients undergoing an elective splenectomy.

Preoperative pulmonary physiotherapy is quite helpful in patients who are debilitated from their hematologic disease, who are immunosuppressed, or who have mediastinal or pulmonary extension of the primary disease as may be present in Hodgkin's disease.

The upper abdominal incision, trauma to the left upper quadrant of the abdomen, and frequent left pleural effusion often lead to significant postoperative atelectasis or pneumonia. The magnitude and significance of the pulmonary complication can be reduced by vigorous preoperative care.

Acutely injured patients who must undergo an abdominal exploration and splenectomy require careful immediate preoperative preparation. When possible, blood volume should be restored prior to induction of the anesthetic. The stomach should be evacuated with a nasogastric tube in order to prevent aspiration. An erect chest x-ray film should be obtained in order to determine the presence of a left pneumothorax or hemothorax. If either is present a thoracostomy tube should be placed prior to induction of the anesthetic.

In cases of massive hemorrhage, or when blood is not available, the autotransfusion apparatus can be utilized for harvesting of intra-abdominal shed blood which can be processed and re-transfused.

Both elective and emergency splenectomy can be carried with a mortality of less than 1 per cent and with a low morbidity if the principles of preoperative care are carried out.

Technique

Splenectomy may be performed using several acceptable techniques. The particular disease or clinical setting should determine the method the surgeon chooses.

The choice of incision depends upon the nature of the disease and the patient's physical configurations. Exposure of the spleen is adequately obtained utilizing a midline, para-median, left subcostal, transverse, or thoracoabdominal incision.

The midline incision is chosen in cases of trauma with suspected rupture of the spleen, liver, stomach, or pancreas. It is easily and rapidly performed, can be extended, and affords good access to the entire upper abdomen. A midline incision is also valuable in patients with severe thrombocytopenia since there is less hemorrhage and less abdominal wall disruption. An incision from the xiphoid to umbilicus is usually adequate in elective splenectomies.

The left para-median incision is preferred by many surgeons for elective splenectomy. If the rectus muscle is well dislocated, one does not damage the muscle and the exposure is excellent. The incision should extend to the costal margin and extend to or just below the umbilicus.

In obese patients, in those in whom there may be adherence in the left upper quadrant, or when the spleen is massive, a left subcostal incision provides good exposure to the spleen. In patients with an acutely angulated costal margin this incision provides better exposure of the spleen with less retraction of the left lateral abdominal wall. This incision may be extended into a bilateral subcostal if further exposure or performance of an accessory operation (cholecystectomy) is necessary.

All these incisions should be large enough so that there is no difficulty with the intra-abdominal manipulation necessary for mobilization of the spleen. Special care should be taken to be sure there is good wound hemostasis. Neglect of this principle may lead to dangerous postoperative hemorrhage or wound hematoma formation in patients with coagulation abnormalities. Careful avoidance of wound hematoma and protection from infection is also important, since many patients who undergo splenectomy have impaired host resistance. A wound infection in such patients may be a life-threatening complication. Closure of the

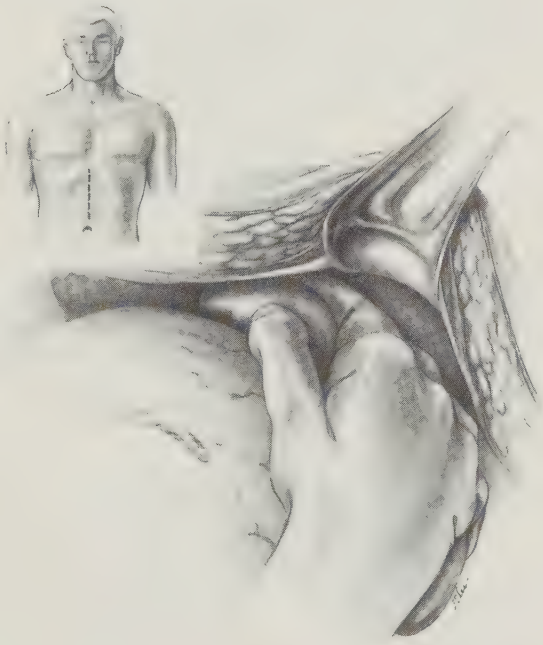

Figure 3. *Splenectomy Step I. Examination of Splenic Mobility.* The right hand is passed between the diaphragm and the spleen to ascertain the size of the spleen, its consistency, and the degree of mobility.

wound should be meticulous and accurate, since many such patients have received corticosteroids which may impair wound healing.

After the abdomen has been opened a rapid thorough exploration is carried out. In hematologic disease such as spherocytosis the presence or absence of gallstones should be specifically noted. In hypersplenism with thrombocytopenia unsuspected cirrhosis of the liver may be encountered. A search for accessory spleens should be made before hematoma or blood staining distorts the gastrosplenic omentum. Accessory spleens are found near the hilus of the spleen, in the gastrosplenic omentum, in the mesenteries of the small intestine and colon, rarely near or in the left testis or ovary, and in the dorsal mesogastrium. An accessory spleen is found in about 20 per cent of autopsies. When splenectomy is indicated and an accessory spleen is found, the accessory spleen should also be excised.

After completion of the exploration, preparation for mobilization and excision of the spleen is made. A nasogastric tube is always placed in order to decompress the stomach and allow easier exposure of the spleen. Both edges of the wound are widely retracted, and any adhesions between the spleen and the anterior abdominal wall, colon, or diaphragm are divided. Further steps in the operation are determined by the size of the spleen, the presence of adhesions between the spleen and the diaphragm, and the length and mobility of the lienorenal ligament.

The right hand should be passed between the diaphragm and the spleen to ascertain the size of the spleen, its consistency, and degree of mobility (Fig. 3). In cases where the spleen is of normal size or when it is quite mobile and with no adhesions the organ can be retracted medially and ventrally. Division of the avascular ligamentous attachments is now performed (Fig. 4). Gentle steady ventromedial traction is maintained in order to tense the ligaments and allow their division. The spleen is gradually delivered into the wound. If tension is encountered, the inferior gastrosplenic ligament and the splenocolic ligaments are divided between ligatures. As the splenorenal ligament is incised loose areolar tissue can be bluntly dissected allowing the entire spleen and its pedicle to move ventrally. When the spleen and its pedicle have been completely mobilized and delivered up to and sometimes through the wound the second stage of the operation is complete (Fig. 5).

The third stage of the operation consists of division of the gastrosplenic omentum including the vasobrevia of the stomach. Each vessel should be individually ligated and divided in order to avoid oozing and hematoma formation (Fig. 6.).

With the spleen quite free the final stage of the operation, ligation and division of the vascular pedicle, can be performed. The pedicle can be isolated from the tail of the pancreas either anterior or posterior to the spleen (Fig. 7). Ideally each vessel is individually ligated and fixed with a transfixion suture. This can be performed either in continuity or subsequent to clamping the vessel. Occasionally because of regional trauma or poor exposure it is necessary to double clamp the entire pedicle, but this technique risks damage to the tail of the pancreas. Mass ligation also risks the potential but rare formation of an arteriovenous fistula.

(*Text continues on page 298*)

Figure 4. *Splenectomy Step II. Division of the Avascular Ligaments.* Gentle steady ventromedial traction allows division of the avascular ligaments and gradual delivery of the spleen into the wound.

Figure 5. *Splenectomy Step III. Division of the Splenocolic Ligament.* The gastrosplenic and gastrocolic ligaments are divided between ligatures when tension is encountered in splenic mobilization.

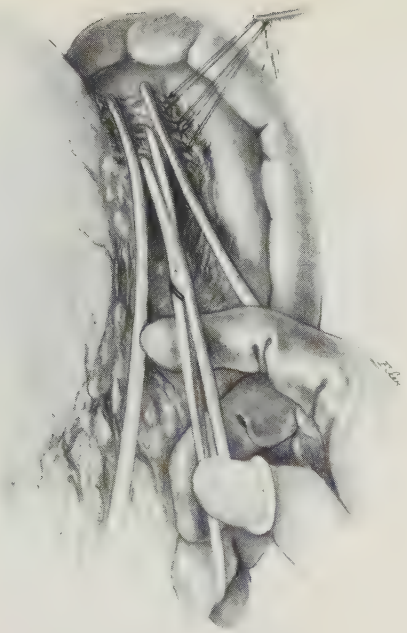

Figure 6. *Splenectomy Step IV. Division of Vasobrevia to the Stomach.* Individual ligation and division of each of the vasobrevia are performed between the greater curvature of the stomach and the upper pole of the spleen.

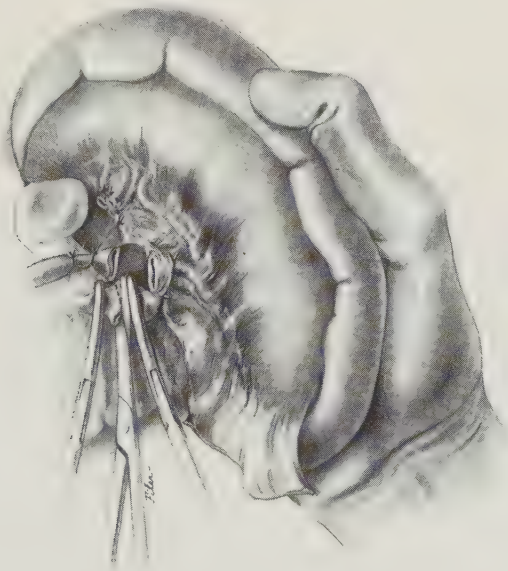

Figure 7. *Splenectomy Step V. Ligation and Division of the Vascular Pedicle.* The vascular pedicle of the spleen can be isolated either anterior or posterior to the spleen but should be free from the tail of the pancreas. Ideally each vessel should be individually ligated and fixed with a transfixion suture.

Figure 8. *Splenectomy Step VI. Inspection of the Splenic Bed.* Careful inspection of the splenic bed is necessary to be sure there is no active hemorrhage. Sites of potential hemorrhage are the diaphragmatic surface, the ligaments, the vasobrevia, and the splenic pedicle.

Following excision of the spleen, careful inspection is performed to be sure there is no hemorrhage. Sources of hemorrhage are the splenic bed and ligaments, especially if there is portal hypertension, the vasa brevia along the greater curvature of the stomach, veins at the gastroesophageal junction and from the splenic pedicle (Fig. 8).

In some cases preliminary ligation of the splenic vessels may be necessary. When the splenic artery has been ligated, there is contraction of the spleen with associated autotransfusion, less blood is lost as the operation proceeds, and the coagulation profile may improve, making oozing less of a problem. Also, the spleen becomes smaller and less dense, and it is easier and safer to mobilize the organ. The best method of preliminary ligation of the splenic artery is to open the lesser omental bursa, retract the stomach, and dissect the splenic artery just distal to its origin from the celiac axis (Fig. 9). Ligation and division are thus carried out preliminary to any dissection. This technique is quite valuable when the spleen is huge or when there are extensive adhesions.

Figure 9. *Preliminary Ligation of the Splenic Artery.* The splenic artery may be ligated preliminarily in the lesser omental bursa close to its origin from the coeliac axis.

Drains should not be utilized unless there has been damage to the tail of the pancreas. In such a situation a sump catheter with suction drainage is preferable and the drain should be removed as soon as drainage diminishes.

COMPLICATIONS

Complications of splenectomy are related to the anatomic location of the spleen, the nature of the condition for which operation has been performed, and the systemic sequelae of splenectomy.

Immediately after operation the most common complication is persistent or recurrent hemorrhage. At reoperation for hemorrhage after evacuation of the hematoma a bleeding site may not always be found. Nevertheless, persistent postoperative hemorrhage should not be treated expectantly. Platelet transfusions and fresh frozen plasma administration are indicated in patients with coagulation disorders and may obviate the need for re-exploration. If correction of coagulation disorders has been accomplished and hemorrhage persists, reoperation is necessary.

The serum amylase should be checked periodically following splenectomy. Transient elevations resolve over the first 2 to 3 postoperative days and are of little concern in the absence of symptoms of pancreatitis. Persistent elevation raises the suspicion of a pseudocyst of the tail of the pancreas. If fever, pleural effusion, or a left upper quadrant air fluid level is present, a subphrenic abscess is likely and surgical drainage as well as systemic antibiotic therapy will be necessary. Subphrenic ab-

scess occurs most frequently in patients who are being treated with immunosuppressive therapy at the time of operation.

Left lower lobe atelectasis with a small pleural effusion is a quite common occurrence following splenectomy and accounts for early postoperative fever. It is the consequence of the left upper quadrant operation, operative trauma, postoperative pain, hypoventilation and diaphragmatic irritation. Vigorous pulmonary physiotherapy following operation diminishes the incidence of this complication.

Following splenectomy there is a rise in leukocyte and platelet count. The thrombocytosis may reach a level of 850,000 to one million platelets. Thrombotic complications are not common, but prophylactic measures to avoid phlebothrombosis or thrombophlebitis should be carried out. Intravenous heparin therapy is not necessary except in patients with previous venous disease or thrombotic complications such as pulmonary embolism.

Splenic vein thrombosis is a rare postoperative complication. It occurs during the second postoperative week when the platelet count has peaked. The symptoms are unexplained abdominal pain and fever. Fatal portal venous thrombosis and mesenteric venous thrombosis have been reported as a consequence of propagation of the splenic thrombus.[24] If the diagnosis is suspected, anticoagulant therapy is indicated in order to prevent propagation of the thrombus. The leukocyte and platelet count gradually return toward normal after splenectomy. Neither anemia nor polycythemia occurs after splenectomy. No long term pathologic complication has been demonstrated. Other reticuloendothelial organs compensate quite adequately for the loss of the spleen.

REFERENCES

1. Ballinger, W., and Erslev, A. J.: Splenectomy, Indications, Technique, Complications. Current Problems in Surgery, Chicago, Yearbook Medical Publishers, 1965, p. 3.
2. Bergin, J. J., Zuck, F. F., and Miller, R. E.: Compelling splenectomy in medically compromised patients. Ann. Surg., *178*:761, 1973.
3. Block, G. E., Evans, R., and Zaithchiem, R.: Splenectomy for idiopathic thrombocytopenic purpura. Arch. Surg., *92*:484, 1966.
4. Brown, H., Soss, M., and Cheng, P.: Infectious mononucleosis and splenic rupture, report of a case. Ohio Med. J., *60*:954, 1964.
5. Collier, H.: Splenectomy, a justifiable operation in leukocythemia. Lancet, 2:1219, 1882.
6. Dameshek, W.: Controversy in idiopathic thrombocytopenic purpura. J.A.M.A., *173*:1025, 1960.
7. Diskinfield, A., and Appenheim, E.: The treatment of acute thrombotic thrombocytopenic purpura with corticosteroids and splenectomy. Arch. Intern. Med., *65*:245, 1966.
8. Eakles, A. J., Kevy, S. V., and Diamond, L. K.: Hazard of overwhelming infection after splenectomy in childhood. New Eng. J. Med., *276*:1225, 1967.
9. Fabri, P., Metz, E. N., Nick, W. V., et al.: A quarter century with splenectomy changing concepts. Arch. Surg., *108*:569, 1974.
10. Fishman, N., and Bollinger, W. F.: Splenectomy for agnogenic myeloid metaplasia and myelofibrosis. Arch. Surg., *90*:246, 1965.
11. Garrison, F. H.: History of Medicine, 4th ed. Philadelphia, W. B. Saunders Co., p. 873, 1929.
12. Johnston, G. B.: Splenectomy with a statistical summary of all reported cases up to 1908. Ann. Surg., *48*:50, 1908.
13. Lewis, M. I., Piruccella, R.: Use of angiography to diagnose subcapsular hematoma of the spleen before delayed rupture. Amer. Surg., *39*:587, 1973.
14. McIntyre, P. A.: Diagnostic significance of the spleen scan. Sem. Nucl. Med., 2:278, 1972.

15. Mayo, W. J.: A review of 500 splenectomies with special reference to mortality and end result. Ann. Surg., *88*:409, 1928.
16. Miller, D. W., and Kelly, D. L.: Splenic trauma, surgical management in children. Arch. Surg., *105*:561, 1972.
17. Moynihan, B. G. A.: The Spleen and Some of Its Diseases. The Bradshaw Lecture of 1920 (The Royal College of Surgeons of England), Philadelphia, W. B. Saunders Co., 1921, p. 4.
18. O'Brien, L.: Case of removal of the spleen without injury or derangement of the animal economy. Med. Chir. J. Recorder, *1*:8, 1816.
19. Pearce, R. M., Krimbhaar, E. B., and Frazier, C. H.: The Spleen and Anemia. Philadelphia, J. B. Lippincott Co., 1918, p. 3, 6, 7, 9.
20. Quittenbaum, K. S.: Commentarii de Splenie Hypertrophie et Historia Extirpationis. Rostock, 1836.
21. Rosch, J.: Roentgenology of the Spleen and Pancreas, Springfield, Illinois, Charles C Thomas, 1967, p. 52.
22. Schwartz, S. I.: Principles of Surgery. New York, McGraw-Hill Book Co., 1969, p. 1148.
23. Schwartz, S. I., Adams, J., and Bauman, A. W.: Splenectomy for Hematologic Disorders. Current Problems in Surgery, May 1971, p. 26, 28.
24. Sweet, R. H.: Total gastrectomy by the transthoracic approach. Ann. Surg., *138*:297, 1953.
25. Tartaglia, A. P.: Thrombotic thrombocytopenic purpura, remission following hemodialysis. J.A.M.A., *218*:999, 1971.
26. Trimble, C., and Eason, F. J.: A complication of splenosis. J. Trauma, *12*:358, 1972.
27. Wells, S.: Enlarged spleen excised during life. Medical Times and Gazette, *1,2*:2, 1866.
28. Whitley, L.: The surgery of the spleen. Lancet, *1*:625, 1952.

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Gastrinomas

Gastrin-Producing Tumors

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The first report by Robert M. Zollinger and Edwin H. Ellison[58, 59] in 1955 of two patients with primary jejunal ulcerations, marked gastric acid hypersecretion, and islet cell tumor of the pancreas focused attention on this unusual triad of clinical findings. Less than 1 per cent of all patients with peptic ulcer will be found to have Zollinger-Ellison syndrome. In 1964, Ellison and Wilson[9] established a registry of patients with proven gastrinomas which presently contains nearly 1000 patients. Because of the data analysis made possible through this tumor registry, it has been established that the majority of patients harboring a gastrinoma have a history, physical findings, and x-ray studies typical of the patient with an ordinary chronic duodenal ulcer.[54] Performance of a vagotomy and either an antrectomy or a drainage procedure for duodenal ulcer in a patient harboring a gastrinoma is inadequate because the primary operation for patients with the Zollinger-Ellison syndrome is total gastrectomy.[12] The target organ of the gastrin-producing tumor, the stomach, must be removed since 59 per cent of gastrinomas of the pancreas are malignant and the opportunity of finding a single excisable tumor of the pancreas is less than one in four.[54]

The development of gastrin radioimmunoassay systems by several investigators[5, 6, 29, 41, 57] has made it possible to make the definitive diagnosis of a gastrinoma by measurement of serum and tumor tissue gastrin levels. The measurement of serum gastrin levels is the only definitive test for the preoperative diagnosis of the presence of a gastrinoma. Gastrin radioimmunoassay of tumor tissue may also be helpful in distinguishing the microscopically similar carcinoid from non-beta islet cell tumors. Serum gastrin determinations are now available to most physicians. However, the interpretation of levels of serum or tissue gastrin in patients before and after operations for customary varieties of gastrointestinal disease has not yet been established. Eight years of experience with gastrin radioimmunoassay systems has permitted accumulation of over 240 subjects with customary varieties of gastrointestinal disease

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for baseline data and comparison to those patients with a gastrinoma (Table 1).

As physicians become more familiar with the earlier manifestations of the Zollinger-Ellison syndrome, it is important to use tests which allow early diagnosis. Perhaps because of growing awareness on the part of the clinicians, the Zollinger-Ellison syndrome and multiple endocrine adenomatosis syndrome are being diagnosed more frequently. It is unlikely that large numbers of patients with Zollinger-Ellison syndrome are currently undetected. Overt cases are probably rather promptly detected because of the current high interest in the disorder.

One purpose of this paper is to alert the physician to a number of unusual clinical situations in which a patient may be harboring a gastrinoma of the pancreas, requiring primary total gastrectomy. These patients may then be differentiated from more numerous patients with either ordinary peptic ulcer or other rare associated endocrinopathy, i.e., parathyroid gastrinoma, requiring a lesser or different type of operative management. The second purpose is to define the clinical situations in which gastrin determinations should be obtained from those more frequent occasions when the physician need not necessarily obtain a "routine" or an "emergency" serum gastrin measurement.

DIAGNOSIS

Circumstantial clinical criteria for the Zollinger-Ellison syndrome as a part of a differential diagnosis have been proposed by Friesen[14] and Wilson.[54] Seven categories of patients with unusual or very unusual clinical features will be defined in which the physician should have a high index of suspicion for the presence of a gastrinoma: (1) Chronic duodenal ulcer and marked gastric acid hypersecretion; (2) Neostomal ulcer; (3) Unexplained diarrhea; (4) Peptic ulcer with other endocrine abnormalities, particularly hyperparathyroidism and/or strong family history of these disorders; (5) Peptic ulcer and unusual tumors in unusual locations; (6) Unusual radiologic findings in the gastrointestinal tract; (7) Primary jejunal ulcer.

Chronic Duodenal Ulcer and Marked Gastric Acid Hypersecretion

Zollinger-Ellison syndrome is somewhat more common in males than females (3 : 2). The onset of the first symptoms is most common between the ages of 20 and 50 years, with a mean of 38 years, but gastrinomas have been reported in children from age 7 and in the elderly to age 90. The peptic ulcer diathesis in the Zollinger-Ellison syndrome has been said to have a fulminating clinical course, but this is usually not the case. Nearly 4 of 5 patients have had gastrointestinal symptoms from 1 to 25 years. Seventy per cent of patients with Zollinger-Ellison syndrome first present with pain related to chronic duodenal ulcer. It has been emphasized that the clinical course of the majority of patients initially need not be fulminant. This is probably the primary reason why many patients harboring gastrin-producing tumors are initially treated

as patients with ordinary peptic ulcer. Although the initial presentation of the Zollinger-Ellison syndrome may not be fulminant, the majority of patients will have a long and catastrophic subsequent clinical course which should be recognized before the patient becomes both a gastrointestinal and psychological cripple. Perforated ulcer, sometimes multiple, has been recently emphasized to be a common occurrence in patients with the Zollinger-Ellison syndrome (31 per cent).[54]

Gastric acid secretory function studies may not be important to the proper management of some gastrointestinal disease but they are pertinent in the diagnosis of Zollinger-Ellison syndrome. It has been shown that a 1 hour fasting or basal gastric juice collection (BAO) followed by a 1 hour augmented histamine stimulation (MAO) are the most reliable tests for gastric secretory function when done under standard conditions by well trained personnel.[37] However, measurement of 12 hour overnight gastric juice collection may also be informative in the diagnosis of the marked gastric hypersecretion characteristics of Zollinger-Ellison syndrome. None of the gastric acid secretory criteria is absolutely diagnostic.

The role of acid secretory testing in diagnosis is an adjunct to identify those patients in whom there is indication for further evaluation, i.e., serum gastrin measurements. Although marked gastric acid hypersecretion has been said to be the hallmark of Zollinger-Ellison syndrome, hypersecretion may not be pronounced.

Wide variations in rates of gastric acid secretion occur at different times in individual patients with the Zollinger-Ellison syndrome.[56] Because the gastric acid levels in patients are not consistently elevated, repetition of gastric analysis is advisable. A 1 hour fasting acid collection of greater than 15 mEq (85 per cent of patients with Zollinger-Ellison syndrome) or 12 hour overnight secretion volume of greater than 1000 ml and 100 mEq of HCl (more than 75 per cent of patients with Zollinger-Ellison syndrome) appears as the best screening test for the diagnosis of Zollinger-Ellison syndrome. Less than seven per cent of patients with duodenal ulcer tested in our gastroenterologic laboratory fall into this range. Serum gastrin measurements should be obtained in all patients with duodenal ulcer and gastric acid hypersecretion and will easily differentiate those with Zollinger-Ellison syndrome from patients with usual duodenal ulcer (Table 1).

Seventy per cent of patients with the Zollinger-Ellison syndrome will have a BAO/MAO ratio of greater than 0.6, because increased circulating gastrin in patients with gastrinomas stimulates fasting acid secretion levels that may be equal to that obtained after histamine stimulation. Polacek and Ellison[33] have demonstrated the gastric parietal cell mass in patients to be more than six times that measured in normal stomachs. Since the maximum histamine acid response is directly proportional to the parietal cell mass, this accounts for the extremely high maximum histamine acid response in patients with gastrinomas.

In contrast to the direct relationship between hypersecretion and hypergastrinemia in patients with the Zollinger-Ellison syndrome, Trudeau and McGuigan[48] have reported an inverse relationship between

Table 1. *Acid and Serum Gastrin in Gastrointestinal Disease*

	FASTING			HISTAMINE-STIMULATED			POST-PRANDIAL (30 min.)	
TYPE OF PATIENT	No. Pts.	Acid mEq/hr	Serum Gastrin pg/ml	No. Pts.	Acid mEq/hr	Serum Gastrin pg/ml	No. Pts.	Serum Gastrin pg/ml
Normal	32	2.2 ± S.E. 0.4	45 ± S.E. 11	31	16.8 ± S.E. 2.4	47 ± S.E. 9	3	75 ± S.E. 30
Gastric Ulcer	22	2.1 ± 0.8	29 ± 19	15	19.5 ± 2.4	38 ± 20	2	73 ± 26
Duodenal Ulcer	60	5.4 ± 1.0	39 ± 9	51	34.2 ± 3.2	41 ± 10	11	63 ± 38
Reflux Esophagitis	39	2.1 ± 0.4	36 ± 10	36	21.2 ± 2.0	59 ± 21	9	55 ± 18
ZES	3	>15	2,293 ± 440					

fasting serum gastrin concentrations and rates of gastric hydrochloric acid secretion in control subjects and patients with assorted gastrointestinal disease. We have found no relationship between BAO and MAO and serum gastrin levels in patients without Zollinger-Ellison syndrome (Table 2). Also, in contrast with the report of McGuigan and Trudeau,[28] there is no significant difference in the fasting, histamine-stimulated and post-prandial serum gastrin levels in patients with ordinary gastrointestinal disease (Table 1).

Neostomal Ulcer

In 60 per cent of patients with the Zollinger-Ellison syndrome, the correct diagnosis is not ascertained at the time of the first operation for peptic ulcer. The diagnosis should be considered when a patient demonstrates continued gastric hypersecretion or neostomal ulcer (usually multiple and penetrating or perforating) following a standard operation for peptic ulcer. It has been stated that most stomal ulcers occurring after inadequate surgical procedures for ordinary peptic ulcer occur months or years after the initial operation whereas stomal ulceration is prompt when gastrinoma is overlooked.[14] That this is not necessarily true can be seen in Case 1 reported in this paper. After gastrojejunostomy, measurements of gastric acid secretory function are often inaccurate because of reflux of jejunal contents. Acid hypersecretion persists because of continued gastrin release by the tumor which is not significantly affected by vagotomy. The uncontrolled gastric acid hypersecretion leading to ulceration of a gastrojejunal stoma is much more commonly caused by an incomplete vagotomy, to an inadequate gastric resection without vagotomy, or to a retained or excluded antrum. Other operative procedures which may be followed by the development of a neostomal ulcer are antrectomy without vagotomy, subtotal gastrectomy without vagotomy, and vagotomy plus gastroenterostomy. Obviously, these cases must be differentiated from those patients with a gastrinoma. The history and physical examination, gastrointestinal tract fluoroscopy tests for completeness of vagotomy and serum gastrin levels constitute the diagnostic approach. Differentiation between ordinary neostomal ulcer and patients also harboring a gastrinoma may be difficult, as is demonstrated in Case 1, a patient with Zollinger-Ellison syndrome. Data concerning the level of serum gastrin in patients with ordinary neostomal ulcer without gastrinoma has been lacking. Table 3 shows the fasting

Table 2. *Serum Gastrin Levels and Rates of Gastric Acid Secretion*

FASTING			HISTAMINE STIMULATED		
No. Patients	Acid mEq/hr	Serum Gastrin pg/ml	No. Patients	Acid mEq/hr	Serum Gastrin pg/ml
87	0 ↔ 1.9	48 ± 1.3 S.E.	35	0 ↔ 9.9	32 ± 7.7 S.E.
37	2.0 ↔ 3.9	48 ± 1.9	32	10 ↔ 19.9	43 ± 11.6
27	>4.0	52 ± 2.3	50	>20.0	54 ± 13.3

Table 3. *Acid and Serum Gastrin after Gastrointestinal Operations*

TYPE OF PATIENT	FASTING			HISTAMINE-STIMULATED			POST-PRANDIAL (30 min.)	
	No. Pts.	Acid mEq/hr	Serum Gastrin pg/ml	No. Pts.	Acid mEq/hr	Serum Gastrin pg/ml	No. Pts.	Serum Gastrin pg/ml
Normal	32	2.2 ± S.E. 0.4	45 ± S.E. 11	31	16.8 ± S.E. 2.4	47 ± S.E. 9	3	75 ± S.E. 30
Post-Op Vagotomy Pyloroplasty	9	2.3 ± 1.1	23 ± 17	8	9.2 ± 3.8	77 ± 29	1	0
Post-Op Billroth I	10	1.0 ± 0.4	36 ± 29	10	7.0 ± 2.3	76 ± 37	2	0 ± 0
Post-Op Billroth II	25	1.0 ± 0.3	68 ± 19	21	7.5 ± 2.2	62 ± 23	5	44 ± 22
Proven Neostomal Ulcers	7	0.7 ± 0.4	54 ± 16	7	3.9 ± 1.4	54 ± 43	0	–
ZES	3	15	2,293 ± 440					

acid and serum gastrin levels in patients with usual neostomal ulcer without gastrinoma of the pancreas. Although somewhat higher than non-ulcer patients, they are significantly lower than patients with Zollinger-Ellison syndrome.

CASE 1. A 53 year old man admitted to the hospital with recurrent upper abdominal pain had had three previous operations for ulcer and two for recurrent ventral hernia. On physical examination there was marked tenderness in the entire epigastrium. No masses were palpable. There was a large ventral hernia measuring 20 cm in diameter.

Past history showed that 8 years prior to this admission the patient had undergone hemigastrectomy and gastrojejunostomy for duodenal ulcer with complete obstruction. Two years later, the patient was admitted for gastrointestinal bleeding and severe abdominal pain which were treated medically. Three years following his initial gastric surgery, a gastrectomy and gastroenterostomy were done for a large posterior neostomal ulcer with complete obstruction. Two years following this procedure, the patient was admitted with a diagnosis of bleeding from neostomal ulceration. The upper gastrointestinal roentgenogram showed two neostomal ulcers with a partial gastric outlet obstruction. He was discharged on medical therapy.

He was re-admitted two months later with severe abdominal pain, nausea, vomiting and melena. An upper gastrointestinal roentgenogram again showed a large ulcer crater at the gastrojejunal stoma. Five years following his initial gastric surgery, a third gastrectomy was done for a large neostomal ulcer. A resection of the gastrojejunostomy was performed and a gastroenterostomy done. Three years following this procedure he was admitted to the hospital and a gastroscopic examination showed a large ulcer at the anastomosis site. The patient was found to have serial fasting serum gastrin levels of 1720 pg per ml, 1710 pg per ml, and 985 pg per ml on 3 consecutive days. (Normal less than 50.)

At operation, now 8 years following his initial gastric surgery, a huge anterior gastric ulcer, 3 cm in diameter, was found penetrating into the abdominal wall and in addition, there were two large stomal ulcers at the site of his previous gastrojejunostomy. A total gastrectomy was carried out. The pancreas was carefully palpated except for the head, where there were dense adhesions, and no tumors could be felt. The liver was free of metastatic disease. Postoperatively, the patient's personality changed entirely, he was eating 6 meals and has maintained his weight.

Comment. From the time of his initial gastric surgery, this patient had an 8 year history of recurrent neostomal ulcer with severe abdominal pain, gastrointestinal obstruction and bleeding. Three gastric operations and recurrent ulcer disease had rendered the patient a gastrointestinal and psychological cripple. The initial operation was for what seemed to be ordinary peptic duodenal ulcer. Because of this long and catastrophic history, at least a gastric analysis should have been obtained. Serial serum gastrin levels along with the patient's history were diagnostic of Zollinger-Ellison syndrome. After careful exploration, no tumor was found.

As in most patients who have had several previous operations, thorough exploration of the pancreas was extremely difficult. It has been stated by Fox[12] and Wilson[54] that if a tumor cannot be found when a patient has markedly elevated serum gastrin levels and high acid secretion suggestive of Zollinger-Ellison syndrome, a distal pancreatectomy should be performed first and the specimen submitted for frozen section to determine the presence of pancreatic hyperplasia or microadenoma-

tosis. Pancreatic hyperplasia or microadenomatosis have been reported as the only component of the Zollinger-Ellison syndrome in some patients. It is possible that associated occult tumors have not been found in these patients.[12] If a tumor is still not found a vagotomy and hemigastrectomy is done.[12, 54] However, the case reported is different in that the patient had multiple previous operations and marked hypergastrinemia. In this case, a tissue diagnosis is not necessary and only primary total gastrectomy is indicated.[12, 54]

Unexplained Diarrhea

Eighteen per cent of patients with Zollinger-Ellison syndrome will first present with symptoms of uncontrollable diarrhea. Thirty per cent of these will eventually develop ulcer symptoms. Cameron and Hoffman[4] have reported that in recent years diarrhea and steatorrhea have been recognized more frequently as initial symptoms in Zollinger-Ellison syndrome. The diarrhea and steatorrhea in patients with the true Zollinger-Ellison syndrome harboring a gastrinoma of the pancreas are due to intestinal hyperperistalsis and failure of activation of fat splitting enzymes caused by the marked gastric acid hypersecretion. This is supported by the observation that gastric aspiration[8] and total gastrectomy[22] will abolish the diarrhea.

There is a group of patients who may present with a diarrheagenic syndrome without gastric acid hypersecretion (not caused by the presence of a gastrinoma and) or the Zollinger-Ellison syndrome. This syndrome has also been called pancreatic cholera or watery diarrhea syndrome.[21] Verner and Morrison[49] described watery diarrhea, hypokalemia, and achlorhydria. Sanzenbacher and co-investigators[38] have proposed that the hormone secretin is elaborated from pancreatic islet cell tumors in patients with diarrhea but without gastric acid hypersecretion. Gastric inhibitory peptide (GIP) and vasoactive intestinal peptide (VIP) have been reported increased in some patients.[3] Serum gastrin is not elevated. The diarrheagenic syndrome can then be easily differentiated by gastric analysis from the Zollinger-Ellison syndrome. Gastrectomy would obviously not benefit these achlorhydric patients.

CASE 2. A 47 year old woman entered the hospital complaining of epigastric pain, nausea, and diarrhea. The patient's epigastric pain was of 12 years' duration. Two gastric ulcers had been documented 4 years earlier. She had been placed on a bland diet and antacid, but returned to the hospital several times because of the severe pain. Two years prior to this admission, the patient began to experience watery diarrhea which responded only moderately to therapy. The patient had no previous gastrointestinal surgery or family history of ulcer diathesis. The patient underwent a psychiatric evaluation prior to her admission.

Physical examination was normal. The upper gastrointestinal roentgenogram showed one gastric ulcer and a large duodenal ulcer, and huge gastric, duodenal, and jejunal folds with mucosal edema suggestive of Zollinger-Ellision syndrome. Diarrhea continued and she became dehydrated. Esophagogastroduodenoscopy showed ulceration of the esophagogastric junction, enlarged gastric folds in the proximal stomach and two large bulbar duodenal ulcers. Gastric secretion volume was 200 ml per hour with a fasting acid output of 51.0 mEq per hour.

Three days following admission, the patient had a sudden onset of severe abdominal pain. A chest roentgenogram showed free air under the diaphragms, suggestive of a ruptured viscus. Just prior to laparotomy, serum gastrin was 2800

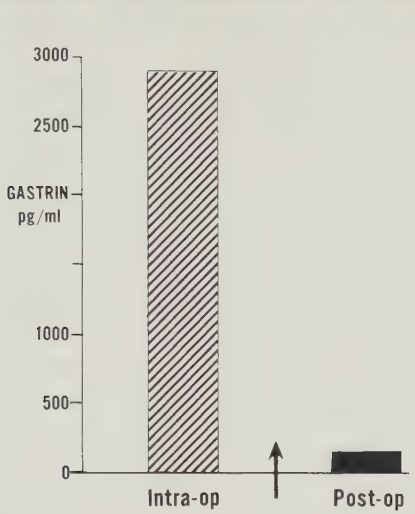

Figure 1. Intraoperative and postoperative serum gastrin levels in a patient with proven Zollinger-Ellison syndrome. Note the decrease to normal 24 hours following removal of a solitary tumor in a lymph node near the head of the pancreas.

pg per ml but the following day after removal of the tumor, the serum gastrin level was almost normal at 113 pg per ml (Fig. 1). Ten days after operation, the patient died from progressive pulmonary insufficiency.

At autopsy, serial sections of the pancreas showed no other primary tumor. Sections of the tumor in the lymph node excised at operation and pancreas removed at autopsy were taken for gastrin radioassay and immunofluorescence. Gastrin content of the pancreas was 136 pg per mg tissue and that in the tumor was 166,000 pg per mg of tissue. The tumor in the lymph node was a non-beta cell adenoma by light microscopy and showed bright gastrin-specific immunofluorescence (Fig. 2).

Comment. This patient had a 12 year history of abdominal pain and ulcer and a 2 year history of diarrhea. Prior to her last hospital admission the patient had no previous operations. Her clinical course was relatively benign for a period of 12 years but within 10 days of the last admission she required an emergency laparotomy for fulminating ulcer disease of the esophagogastric junction, stomach, and duodenum with essentially complete necrosis of the duodenum and perforation. Because of her history, an "emergency" serum gastrin determination before exploratory laparotomy was found to be markedly elevated and diagnostic of the presence of a gastrinoma. A primary total gastrectomy was done and a single lymph node with non-beta islet cell tumor was excised. Within 24 hours postoperatively the serum gastrin level was almost in the normal range. Unfortunately, the patient died and no tumor was found at autopsy. In this case, the surgeon had been able to completely remove the only functioning tumor.

This would seem the ideal situation for tumor excision without gastrectomy which would have in this case halted ulcer diathesis and diar-

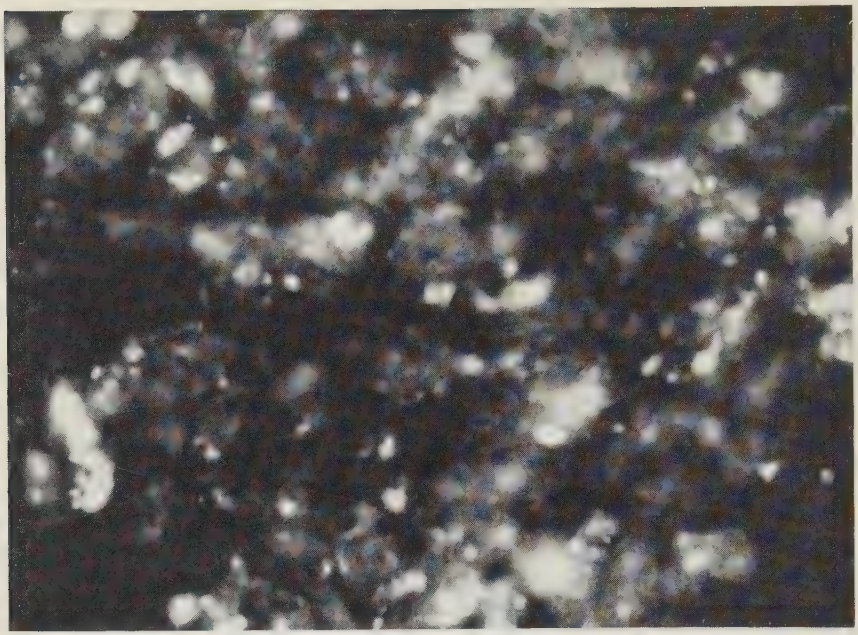

Figure 2. Fluorescent micrograph of the gastrinoma removed from case 2 (ZES). The cytoplasm of the tumor cells are brightly fluorescent specifically due to the presence of gastrin (×53).

rhea. However, because the surgeon could not be sure at the time of operation that he had removed the only tumor, total gastrectomy was his only alternative. Fox and co-authors[12, 13] have reported a 60 per cent survival in patients with local tumor excision without gastrectomy, and 71 per cent survival in patients who had both local tumor excision and total gastrectomy.

The circumstantial clinical manifestations of the Zollinger-Ellison syndrome are variable. Many patients present with acute complications of peptic ulcer such as perforation or hemorrhage requiring immediate operation, thus precluding proper preoperative evaluation. The diagnosis can be suspected in individuals in whom one or more of the circumstantial clinical criteria are present. At the time of emergency operation this should stimulate a careful exploration of the pancreas, liver, duodenum, and enlarged lymph nodes after the emergent situation has been controlled.

A portion of a suspicious and unusual tumor should be frozen for tissue gastrin radioimmunoassay measurement and blood drawn for serum gastrin determination. Even though in the case of an emergency laparotomy, a primary "standard" procedure might seem necessary, a markedly elevated "emergency" serum gastrin level would alert the surgeon that the patient may rather require a primary total gastrectomy as was done in this case. Under certain circumstances the result of a serum gastrin determination may be obtained within 4 hours from the time a blood sample is drawn.

Peptic Ulcer With Other Endocrine Abnormalities

Patients with gastrin-producing pancreatic tumors frequently have both a strong family history of endocrine abnormalities and additional tumors in other endocrine glands, primarily the parathyroids (20 to 50 per cent).[10, 14] Other commonly involved endocrine organs are the pituitary and adrenal glands. This entity of multiple endocrine gland tumors has been termed multiple endocrine adenomatosis (MEA). This has been further subdivided into MEA-1 or Wermer's syndrome (acromegaly, hyperparathyroidism, and gastrinoma)[52] and MEA-II or Sipple's syndrome in which medullary thyroid carcinoma is associated with pheochromocytoma. These confusing classifications may not be justified since it is now apparent that the "classical" Zollinger-Ellison syndrome and parathyroid gastrinoma are only "components or special variants" of the more inclusive multiple endocrine adenomatosis syndrome.[14, 15] Any variety of combinations of different hormone excesses such as gastrin, insulin, glucagon, ACTH, melanocyte-stimulating hormone, serotonin, parathormone, prostaglandins, catecholamines, and follicle-stimulating hormone may be found and have been suggested to be produced by totipotential cells all derived from the embryologic foregut.[14, 21, 30, 32, 38, 44] The variety and combinations of production of these hormones by the tumor will determine the features of clinical presentation.

With the awareness of multiple endocrine adenomatosis and the increasing availability of radioimmunoassays for insulin, gastrin, glucagon, and parathormone, the ability to diagnose this syndrome is becoming mainly a matter of alertness on the part of the physician and thoroughness in obtaining family histories and laboratory studies. Diagnosis is especially rewarding because surgical treatment is direct and demonstrably effective.

An increased incidence of peptic ulceration (8 to 87 per cent) in association with primary hyperparathyroidism both with and without the presence of a non-beta islet cell tumor has been reported.[1, 14, 15] Patients with primary hyperparathyroidism without gastrinoma of the pancreas may occasionally present with elevated serum gastrin levels.[7] The combination of hypergastrinemia and peptic ulcer with hyperparathyroidism might suggest to the clinician that the patient also has a gastrinoma of the pancreas and requires total gastrectomy. However, Stremple and Watson[44] have found that a parathyroid adenoma associated with hyperparathyroidism may produce both parathormone and gastrin, a parathyroid gastrinoma. Parathyroidectomy should be done first since serum gastrin levels will slowly decrease to a normal range. Total gastrectomy is not initially indicated in patients in whom the serum gastrin level decreases to the normal range, although a "standard" ulcer operation may be required for persistent ulcer symptoms. Total gastrectomy may be required after parathyroidectomy if serial serum gastrin levels remain markedly elevated after parathyroidectomy, suggesting an associated gastrinoma of the pancreas.

CASE 3. A 54 year old woman was found to have hyperparathyroidism and a markedly elevated fasting serum gastrin. Before parathyroidectomy, the patient

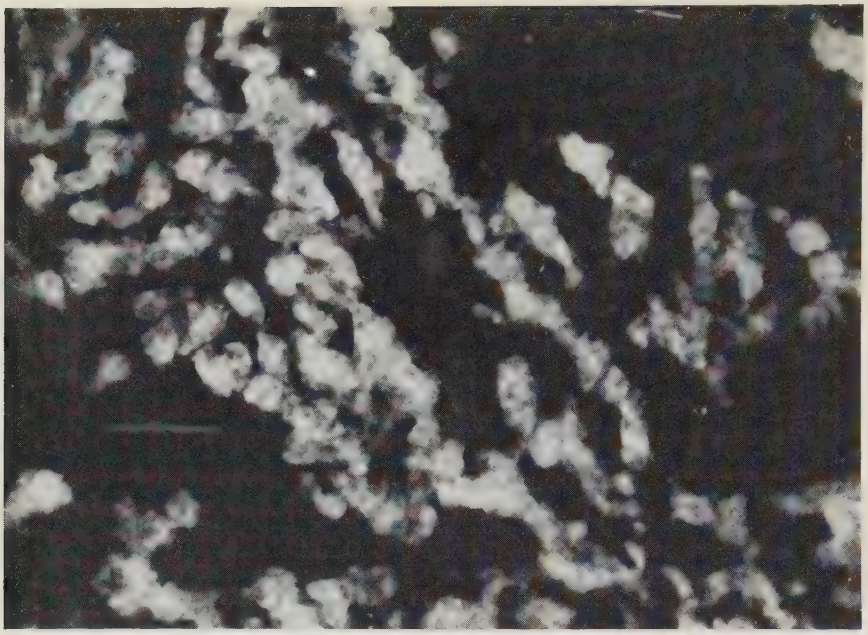

Figure 3. Fluorescent micrograph of the parathyroid gastrinoma removed in case 3. The cytoplasm of cells corresponding to chief cells by hematoxylin and eosin stain are brightly fluorescent specifically due to the presence of gastrin (×53).

was not stimulated with histamine because of severe asthma. Upper gastrointestinal x-ray and gastroscopic exminations showed no evidence of ulcer. There was a family history of peptic ulcers, but not hyperparathyroidism. The patient did not have pernicious anemia.

One week before removal of the left inferior parathyroid adenoma, a blood sample from the left brachiocephalic vein showed a serum gastrin level of 2375 pg per ml; in the peripheral vein the gastrin level was 2035 pg per ml.

The left inferior parathyroid adenoma was surgically removed. The parathyroid adenoma had a tissue gastrin content of 16,216 pg per mg. Parathyroid tissue gastrin content determined by immunofluorescent stain (Fig. 3) correlated with the gastrin content determined by immunofluorescent stain in a non-beta islet cell tumor removed from a different patient with true Zollinger-Ellison syndrome (Fig. 2). The cytoplasm of parathyroid cells corresponding to chief cells by hematoxylin and eosin stain, were brightly fluorescent for the presence of immunoreactive gastrin. Six other parathyroid adenomata from patients with relatively normal serum gastrin levels showed only reddish-yellow autofluorescence.

Three months after the removal of the parathyroid adenoma, mean basal serum gastrin had fallen slightly to 1757 pg per ml.

Twelve months following removal of the parathyroid adenoma mean fasting serum gastrin had fallen significantly in three different daily determinations to 350 pg per ml.

Seventeen months after removal of the parathyroid adenoma, mean serum calcium remained normal at 9.2 mg per 100 ml. Mean fasting serum gastrin decreased from 350 pg per ml to 125 pg per ml in three different daily determinations (Fig. 4). Mean 15 minute postprandial (beef broth) serum gastrin was 295 pg per ml in three different daily determinations. Basal and Histalog-stimulated gastric acid determinations showed no measurable gastric acid. Gastroscopic examination showed grossly normal appearing gastric mucosa. Five separate gas-

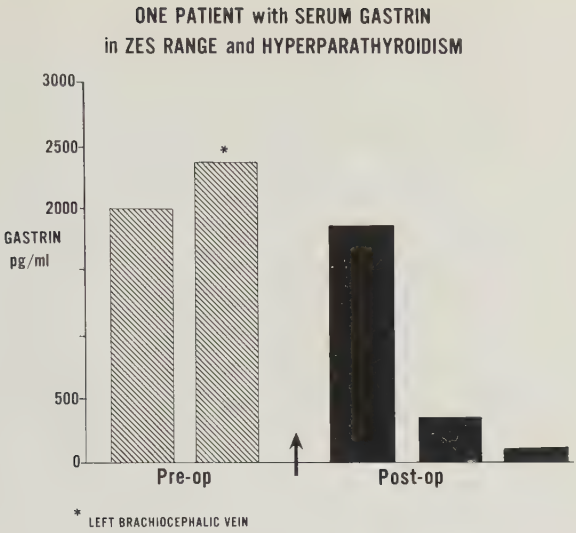

Figure 4. Serial serum gastrin measurements in case 3 before and after parathyroidectomy. Serum gastrin decreased from markedly elevated levels similar to Zollinger-Ellison syndrome postoperatively to a normal range 17 months after removal of a gastrin-producing parathyroid adenoma.

tric mucosal biopsies from the fundus and three from the antrum, reviewed by two different pathologists, showed chronic gastritis with identifiable parietal cells in the fundus, and normal antral mucosa. Antral (G)-cell hyperplasia was demonstrated by both toluidine blue staining and gastrin immunofluorescence. Serum vitamin B_{12} level and Schilling test were normal.

Comment. In this patient with primary hyperparathyroidism, a parathyroid tumor, the vein draining it, and the systemic blood contained excessive amounts of gastrin. The amount of gastrin found in the parathyroid adenoma and serum was similar to that in patients with gastrinoma of the pancreas and the Zollinger-Ellison syndrome. Gastrin was found by immunofluorescence in the cytoplasm of the chief cells of this parathyroid adenoma. After parathyroidectomy, this patient's serum gastrin has decreased to near normal levels. The time lag for the decrease in serum gastrin may be accounted for by antral gastrin (G)-cell hyperplasia and initial release of feedback inhibition of antral gastrin after removal of the parathyroid adenoma. The decrease of serum gastrin level to near normal may be speculated as reverse corollary to the slow decline in elevated serum gastrin after total gastrectomy or parathyroidectomy in patients with gastrinoma of the pancreas.[31, 47]

Although this patient with parathyroid gastrinoma had achlorhydria, easily eliminating Zollinger-Ellison syndrome, a second patient has been studied with hypergastrinemia, gastric acid hypersecretion, and gastrin-producing hyperplasia of the parathyroid. These may suggest a need for total gastrectomy. However, parathyroidectomy should be done first and acid and serum gastrin levels may decrease to the normal range.

Peptic Ulcer and Unusual Tumors in Unusual Locations

Patients may have documented duodenal ulcer in addition to seemingly unrelated and unusual tumors located in unusual locations. Islet cell tumors have been identified in the duodenal wall in 13 per cent of patients in the Zollinger-Ellison tumor registry.[20] The associated findings of a duodenal ulcer and a "carcinoid" tumor should alert the surgeon to the possibility of the Zollinger-Ellison syndrome. Serum and tissue gastrin levels should be determined. On routine staining and light microscopy, the differentiation between carcinoid tumors and non-beta islet cells may be difficult. A portion of the presumed carcinoid tumor should be frozen at the time of removal and gastrin content of the tumor tissue determined by radioimmunoassay and immunofluorescence. The author has had personal experience with one patient who had an emergency operation for gastrointestinal hemorrhage caused by an ulcerated tumor in the duodenum. Under light microscopy differentiation between carcinoid and non-beta islet cell tumor could not be made. Gastrin radioimmunoassay of the tumor showed it to be a carcinoid which contained some gastrin but not in the range found in the gastrinoma. Although a portion of the carcinoid was left behind, a postoperative serum gastrin level was normal. Carcinoid and non-beta islet cell gastrinomas are often associated as a part of multiple endocrine adenomatosis. Therefore, this patient must be followed closely with serial serum gastrin levels in the event that a gastrinoma becomes manifest. Paraduodenal and parapancreatic lymph nodes are frequently involved with non-beta islet cell tumor. Non-beta islet cell tumor is frequently found in a single lymph node near the superior portion of the pancreas without any other primary tumor within the pancreas.

Unusual Radiologic Findings in the Gastrointestinal Tract

Radiologic studies show a duodenal ulcer in 4 of 5 patients with Zollinger-Ellison syndrome; however, a radiologist may be the first to suggest a diagnosis of Zollinger-Ellision syndrome when examining a patient with ulcer or diarrhea because of several unusual radiologic features. These include large gastric rugal folds, giant ulcers of the esophagus, stomach, duodenum, and/or jejunum, and dilation of the duodenum and jejunum with fluid levels and mucosal edema. Pancreatic arteriography may not be helpful in localizing gastrinomas which may be less than 5 mm in diameter. However, Gray and associates[18] have reported a diagnostic accuracy of 60 per cent in islet-cell tumors with arteriography including patients with Zollinger-Ellison syndrome.

Primary Jejunal Ulcer

Primary jejunal ulcer, particularly when perforated in a patient who has not had previous operation, has been said to be pathognomonic of Zollinger-Ellison syndrome.[12] It must be emphasized that jejunal ulceration after trauma and sepsis is a variant of the stress ulcer syndrome and is not related to the presence of a gastrinoma.[42]

The definitive diagnosis of the presence of a gastrinoma is established by markedly elevated fasting serum gastrin levels in a patient

with one or more of the previously mentioned circumstantial clinical features.

Hypergastrinemia alone is not specific for Zollinger-Ellison syndrome. Other clinical situations in which fasting serum gastrin concentrations have been reported elevated in the absence of a gastrinoma are: patients with achlorhydria and adequate vitamin B_{12} absorption, pernicious anemia, or hypochlorhydria and chronic gastritis;[2, 16, 25] peptic ulcer with antral gastrin-(G)-cell hyperplasia;[17, 25] gastric outlet obstruction;[11] short gut syndrome;[40] hyperparathyroidism with gastrinoma of the parathyroid;[44] some cases of renal insufficiency;[23] and patients with pancreatic exocrine insufficiency.[19]

Although serum gastrin concentrations in patients with pernicious anemia may be as high as found in Zollinger-Ellison syndrome, these patients are easily distinguishable because they have achlorhydria. Patients with peptic ulcer, gastric hypersecretion, and hypergastrinemia due to antral gastrin-(G)-cell hyperplasia have been classified Zollinger-Ellison syndrome Type I as compared to patients with gastrinoma and "classic" Zollinger-Ellison syndrome who have been classified as Type II.[34] These may be distinguished by a meal challenge or by antral mucosal biopsy. Patients with Zollinger-Ellison syndrome do not respond to a meal challenge by increased serum gastrin whereas patients with ordinary peptic ulcer and antral gastrin-(G)-cell hyperplasia have a marked increase in serum gastrin after feeding.[34] Calcium or secretin infusion tests may also be useful in separating patients with peptic ulcer and antral-gastrin-(G)-cell hyperplasia from those with Zollinger-Ellison syndrome. Patients with acute erosive gastritis from ethanol or aspirin abuse do not have elevated serum gastrin levels.

Patients with the short gut syndrome who may have gastric hypersecretion and hypergastrinemia will also respond to a meal challenge with an increased serum gastrin concentration.[40] In five patients with the short gut syndrome fasting serum gastrin concentrations were lower than the usual patient with Zollinger-Ellison syndrome and ranged from 300 to 525 pg per ml.

Patients with gastric outlet obstruction may have serum gastrin levels two to three times normal which may overlap values found in Zollinger-Ellison syndrome. These may be distinguished from patients with Zollinger-Ellison syndrome by repeated serum gastrin measurement after nasogastric suction and gastric decompression.

A patient with parathyroid gastrinoma may be distinguished from Zollinger-Ellison syndrome if after parathyroidectomy serum gastrin falls to normal.

Studies with 9 anephric patients showed fasting serum gastrin levels to be highly variable, ranging from a low of 10 pg per ml to a high of 800 pg per ml with a mean of 208 pg per ml. This is much higher than that found in normal subjects and occasionally may be considered in the range of Zollinger-Ellison syndrome.

Pancreatic exocrine deficiency in man has been found associated with very high fasting levels of cholecystokinin-pancreozymin,[19] which cross-reacts with gastrin in some radioimmunoassay systems[43] and,

therefore, an apparent elevated gastrin level may be found in these patients.

Fasting, feeding, and histamine does not significantly elevate serum gastrin levels in patients with ordinary gastric or duodenal ulcer, or reflux esophagitis from that found in normal patients (Table1). Patients who have had vagotomy and pyloroplasty, antrectomy with gastroduodenostomy, or gastrojejunostomy and neostomal ulcer have significantly lower serum gastrin levels than patients with Zollinger-Ellison syndrome (Table 3).

The most common cause of inappropriate hypergastrinemia is gastrinoma. Since fasting serum gastrin concentrations may vary in Zollinger-Ellison syndrome, there have been great differences of opinion as to the serum gastrin concentration which is diagnostic for the presence of Zollinger-Ellison syndrome even when the other causes for hypergastrinemia have been excluded. Fasting serum gastrin concentrations have been reported to range from 100 to 400,000 pg per ml.[50] The very high values have been found in patients with liver metastases. Lower serum gastrin values are found in patients with a small duodenal gastrinoma, gastrinomas confined to the pancreas, or with metastasis confined to local lymph nodes.

McGuigan[27] has used a fasting gastrin value of greater than 300 pg per ml whereas Wilson[54] has used a fasting serum gastrin value of greater than 750 pg per ml as suggestive of the Zollinger-Ellison syndrome. Isenberg and co-authors[21] have stated that serum gastrin levels may be normal or intermittently normal or normal until provoked by calcium or secretin. Therefore, these patients with "latent" gastrinomas cannot be diagnosed by measurement of fasting serum gastrin alone. Some patients[31, 35] have been found to have non-beta islet cell tumors and had a fasting serum gastrin level as low as 100 pg per ml. Of 60 patients from the tumor registry in whom serum gastrins were determined, none had levels below 1000 pg per ml.[53] There is general agreement[2, 21, 27, 43, 45, 50] that serial fasting serum gastrin levels of 1000 pg per ml or greater plus marked gastric acid hypersecretion and the previously mentioned clinical features establishes the diagnosis of Zollinger-Ellison syndrome in the great majority of cases and no additional information is needed. Because a small group of patients has been reported with gastric hypersecretion and borderline hypergastrinemia who have been found to harbor a "latent" gastrinoma, various stimulation and suppression tests have been proposed to gain additional information and "unmask" the presence of a gastrinoma. These include measurement of the integrated serum gastrin response to meals, calcium, and secretin.

In some patients with ordinary peptic ulcer, marked hypergastrinemia in the Zollinger-Ellison syndrome range has been demonstrated. This is due to antral gastrin-(G)-cell hyperplasia and overactivity of the antral mucosa.[17] Normal subjects and patients with ordinary peptic ulcer show moderate increases in mean serum gastrin concentrations after feeding (Table 1). Berson and Yalow[2] concluded that when a patient has moderate borderline hypergastrinemia and hyperchlorhydria, a feeding test is all that is needed to separate these patients from those with Zol-

linger-Ellison syndrome. The test meal which most regularly causes significant increase in serum gastrin level in normal subjects is one rich in protein such as beef broth.[24]

The results of calcium stimulation tests on acid and serum gastrin levels in normal subjects, in patients with duodenal ulcer, and in patients with Zollinger-Ellison syndrome have been reported by Passaro and associates[31] and others.[35] This test involves the rapid intravenous infusion of calcium and serial measurement of gastric acid output and serum gastrin levels. Patients with very low fasting gastrin levels but with gastrinoma respond with a pronounced rise in both acid secretion and serum gastrin concentration. Passaro and associates[31] have concluded that the calcium infusion test has aided in the diagnosis of the Zollinger-Ellison syndrome especially when fasting serum gastrin was not in the diagnostic range. An increase in serum gastrin to more than 500 pg per ml representing a two-fold or greater increase over the fasting gastrin level with calcium infusion is considered the criterion diagnostic for the presence of a gastrinoma and has always been associated with gastrinoma according to Walsh.[50] Although the increase in serum gastrin is not as great, calcium infusion increases serum gastrin concentration in patients with duodenal ulcer and hypergastrinemia due to antral gastrin-(G)-cell hyperplasia and thus may not always differentiate these patients from those with Zollinger-Ellison syndrome.[31, 36] In addition, the calcium infusion test is time consuming and is not without hazard from cardiac arrhythmias. Although Passaro has stated there are no known deaths reported in the literature due to calcium infusion, he also stated that the test should not be performed in patients with cardiac or renal disease or in those receiving cardiac glycosides.[31] Because of the risk and the very few patients in whom it is really necessary for the diagnosis of Zollinger-Ellison syndrome, most gastroenterologists are not anxious to do calcium infusion studies.

The response of serum gastrin levels to secretin infusion may be a more accurate diagnostic tool for Zollinger-Ellison syndrome.[46] Certainly it is a simpler and safer procedure. Secretin infusion suppresses the release of antral gastrin following a meal in normal subjects and those with duodenal ulcer, including those with hypergastrinemia due to antral gastrin-(G)-cell hyperplasia but stimulates release of gastrin in patients with Zollinger-Ellison syndrome. Korman and co-workers[26] distinguished a patient with retained antrum from gastrinoma by employing a secretin infusion test. At the present time both the calcium infusion test and the secretin test have limited value. They should not be considered screening tests. More data relating to the efficacy of these tests must be accumulated.

TREATMENT

It has been reported that the ulcer symptoms of some patients with Zollinger-Ellison syndrome may be "temporarily" controlled for considerable periods of time by a combination of antacid and anticholinergic

therapy.[21, 39] However, it has been well established that mortality is six times higher when primary total gastrectomy has been performed on an emergency basis. Wilson[54] has stated that patients treated medically invariably have developed complications of gastric hypersecretion. The major cause of death is related to the ulcer diathesis, though 60 per cent of gastrinomas of the pancreas are malignant and 80 per cent are associated with metastasis. Only total gastrectomy or complete removal of the gastrinoma will prevent progression of the ulcer diathesis with the complications of hemorrhage and perforation which are the major causes of death in patients with Zollinger-Ellison syndrome. Owing to the frequency of multiple occult tumors and metastases, rarely does the surgeon have option for treatment by local excision of tumor alone.

The estimation of "emergency" serum gastrin level by the most rapid radioimmunoassay technique presently available and under the best logistic situation requires at least 4 hours from the time the serum sample is drawn. This may delay the operation but may afford the opportunity for more logical and expeditious decision making.

Cumulative data from the Zollinger-Ellison syndrome tumor registry on 243 patients with proven metastatic tumor showed that 63 per cent survived after total gastrectomy and only 31 per cent survived after procedures less than total gastrectomy.[12, 13] Cameron and Hoffman[4] reported 7 of 8 patients without metastasis were alive 7 years after total gastrectomy and 3 of 7 patients with metastatic tumor were alive 10 years after total gastrectomy. Furthermore, after total gastectomy only 13 per cent of patients died from tumor progression, whereas after lesser gastric operations 21 per cent died from tumor progression.[12, 13] The gastrinoma of the pancreas in Zollinger-Ellison syndrome is unique in that there seems to be a "gastric feedback" factor in the stomach controlling tumor growth which accounts for regression or lack of progression of the gastrinoma after removal of the stomach.[14]

These data clearly establish that primary total gastrectomy is the procedure of choice in children and adults with malignant Zollinger-Ellison tumors, especially in the presence of widespread metastasis. Primary total gastrectomy is also indicated in patients who had multiple operations for neostomal ulceration even if no tumor is found and in the patient who has a single localized tumor that can be easily removed.[12, 13, 20, 55]

SUMMARY

Several clinical situations suggest gastrinoma of the pancreas and Zollinger-Ellison syndrome. The more common are chronic duodenal ulcer and marked gastric acid hypersecretion, neostomal ulcer after any of the standard ulcer operations, unexplained diarrhea, and peptic ulcer with other endocrine abnormalities, particularly hyperparathyroidism. In these cases, the physician should obtain fasting and postprandial serum gastrin measurements, which will establish the diagnosis of Zollinger-Ellison syndrome in the majority of cases. Primary total gastrectomy is

the procedure of choice for the treatment of Zollinger-Ellison syndrome in both children and adults.

The reader is encouraged to report documented cases to Dr. Stuart D. Wilson, Zollinger-Ellison Tumor Registry, Division of Surgery, The Medical College of Wisconsin, Milwaukee, Wisconsin 53226.

REFERENCES

1. Ballard, H., Frame, B., and Harstock, R.: Familial multiple endocrine adenoma peptic ulcer complex. Medicine, *43*:481, 1964.
2. Berson, S. A., and Yalow, R. S.: Radioimmunoassay in gastroenterology. Gastroenterology, *62*:1061, 1972.
3. Bloom, S. R., Polak, J. M., and Pearse, A. G.: Vasoactive intestinal peptide and watery diarrhea syndrome. Lancet, 2:14, 1973.
4. Cameron, A. J., and Hoffman, H. N.: Zollinger-Ellison syndrome: Clinical features and long-term follow-up. Mayo Clin. Proc., *49*:44, 1974.
5. Chan Yip, B. S., and Jordan, P.: Radioimmunoassay of gastrin using antiserum to porcine gastrin. Proc. Soc. Exper. Biol. Med., *134*:380, 1970.
6. Charters, A. C., Odell, W. D., Davidson, W. D., et al.: Gastrin immunochemical properties and measurement by radioimmunoassay, Surgery, *66*:104, 1969.
7. Dent, J. R., Wang, C., Deftos, L., et al.: Hyperparathyroidism: Gastric acid secretion and gastrin. Ann. Surg., *176*:360, 1972.
8. Donaldson, R. M., Von Eigen, P. R., and Dwight, R. W.: Gastric hypersecretion, peptic ulceration and islet cell tumor of pancreas (Zollinger-Ellison syndrome). New Eng. J. Med., *257*:965, 1957.
9. Ellison, E. H., and Wilson, S. D.: The Zollinger-Ellison syndrome: Reappraisal and evaluation of 260 registered cases. Ann. Surg., *160*:512, 1964.
10. Ellison, E. H., and Wilson, S. D.: The Zollinger-Ellison syndrome updated. Surg. Clin. N. Amer., *47*:115, 1967.
11. Feurle, G., Ketterer, H., Becker, H. D., et al.: Circadian serum gastrin concentrations in control persons and in patients with ulcer disease. Scand. J. Gastroenterol., *7*:177, 1972.
12. Fox, P. S., Hofman, J. W., Wilson, S. D., et al.: Surgical management of the Zollinger-Ellison syndrome. Surg. Clin. N. Amer., *54*:395, 1974.
13. Fox, P. S., Hofman, J. W., DeCosse, J. J., et al.: The influence of total gastrectomy on survival in malignant Zollinger-Ellison tumors, Ann. Surg., 1974.
14. Friesen, S. R.: Zollinger-Ellison syndrome. *In* Ravitch, M., ed.: Current Problems in Surgery. Chicago, Year Book Medical Publishers, April 1972.
15. Friesen, S. R., Schimke, R., and Pearse, A. G.: Genetic aspects of the ZE syndrome: Prospective studies in two kindred; antral gastrin cell hyperplasia. Ann. Surg., *176*:370, 1972.
16. Ganguli, P. C., Cullen, D. R., and Irvine, W. J.: Radioimmunoassay of plasma gastrin in pernicious anemia, achlorhydria without pernicious anemia, hypochlorhydria, and in controls. Lancet, *1*:155, 1971.
17. Ganguli, P. C., Pearse, A. G., Polak, J. M., et al.: Antral-gastrin-cell hyperplasia in peptic-ulcer disease. Lancet, *1*:583, 1974.
18. Gray, R. K., Rosch, J., and Grollman, J. H.: Arteriography in the diagnosis of islet-cell tumors. Radiology, *97*:39, 1970.
19. Harvey, R. F., Hartog, M., Dowsett, L., et al.: A radioimmunoassay for cholecystokinin-pancreozymin. Lancet, 2:826, 1973.
20. Hofman, J. W., Fox, P. S., and Wilson, S. D.: Duodenal wall tumors and the Zollinger-Ellison syndrome. Arch. Surg., *107*:334, 1973.
21. Isenberg, J. I., Walsh, J. H., and Grossman, M. I.: Zollinger-Ellison syndrome. Gastroenterology, *65*:140, 1973.
22. Jesseph, J. E., Moore, F. T., and Passi, R. B.: Peptic ulceration and enteritis. Amer. J. Surg., *113*:188, 1967.
23. Korman, M. G., Laver, M. C., and Kansku, J.: Hypergastrinemia in chronic renal failure. Brit. Med. J., *1*:209, 1972.
24. Korman, M. G., Soveny, C., and Hansky, J.: Effect of food on serum gastrin evaluated by radioimmunoassay. Gut, *12*:619, 1971.
25. Korman, M. G., Strickland, R. G., and Hansky, J.: Serum gastrin in chronic gastritis. Brit. Med. J., 2:16, 1971.

26. Korman, M. G., Scott, D. F., Hansky, J., et al.: Hypergastrinemia due to excluded gastric antrum: a proposed method for differentiation from the Zollinger-Ellison syndrome. Austral. New Zeal. J. Med., *3*:266, 1972.
27. McGuigan, J. E.: The Zollinger-Ellison syndrome and related disease. *In* Sleisenger, M., and Fordtran, J., eds.: Gastrointestinal Disease. Philadelphia, W. B. Saunders Co., 1973.
28. McGuigan, J. E., and Trudeau, W. L.: Difference in rates of gastrin release in normal persons and patients with duodenal-ulcer disease. New Eng. J. Med., *288*:64, 1973.
29. McGuigan, J. E., and Trudeau, W. L.: Immunochemical measurement of elevated levels of gastrin in serum of patients with pancreatic tumors of the Zollinger-Ellison variety. New Eng. J. Med., *278*:1968.
30. O'Neal, L., Kipnis, D., Luse, S., et al.: Secretion of various endocrine substances by ACTH-secreting tumors—gastrin, melanotropin, norepinephrine, serotonin, parathormone, vasopressin, glucagon. Cancer, *21*:1219, 1968.
31. Passaro, E., Basso, N., and Walsh, J. H.: Calcium challenge in the Zollinger-Ellison syndrome. Surgery, *72*:60, 1972.
32. Pearse, A. G.: The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic, and pathologic implications of the concept. J. Histochem. Cytochem., *17*:303, 1969.
33. Polacek, M. A., and Ellison, E. H.: Parietal cell mass and gastric acid secretion in the Zollinger-Ellison syndrome. Surgery, *60*:606, 1966.
34. Polak, J. M., Stagg, B. H., and Pearse, A. G.: Two types of Zollinger-Ellison syndrome: Immunofluorescent, cytochemical and ultrastructure studies in different clinical states. Gut, *13*:501, 1972.
35. Reeder, D. D., Becker, H. D., and Thompson, J. C.: Effect of intravenously administered calcium on serum gastrin and gastric secretion in man. Surg. Gynec. Obstet., *138*:847, 1974.
36. Reeder, D. D., Jackson, M., Ban, J., et al.: Influence of hypercalcemia on gastric secretion and serum gastrin concentrations in man. Ann. Surg., *172*:540, 1970.
37. Ruckley, C. V., and Sircus, W.: Test for gastric secretory function and their clinical applications. *In* Glass, G. B. J., ed.: Progress in Gastroenterol., Vol. III. New York, Grune and Stratton, 1970, pp. 73–89.
38. Sanzenbacher, L., Mekhjian, H., King, D., et al.: Studies on the potential role of secretin in the islet cell tumor diarrheagenic syndrome. Ann. Surg., *176*:394, 1974.
39. Shimoda, S. S., and Rubin, C. R.: The Zollinger-Ellison syndrome with steatorrhea, I. Anticholinergic treatment followed by total gastrectomy and colonic interposition. Gastroenterology, *55*:695, 1968.
40. Straus, E., Gerson, C., and Yalow, R. S.: Hypersecretion of gastrin associated with short bowel syndrome. Gastroenterology, *66*:175, 1974.
41. Stremple, J. F., and Meade, R. C.: Production of antibodies to synthetic human Gastrin I and radioimmunoassay of gastrin in the serum of patients with the Zollinger-Ellison syndrome. Surgery, *64*:165, 1968.
42. Stremple, J. F., Mori, H., Lev, R., et al.: The stress ulcer syndrome. *In* Ravitch, M., ed.: Current Problems in Surgery. Chicago, Year Book Med. Publ., April 1973.
43. Stremple, J. F., and Meade, R. C.: Radioimmunoassay of hormones associated with the pancreas. *In* Carey, L. C., ed.: The Pancreas. St. Louis, C. V. Mosby Co., 1973.
44. Stremple, J. F., and Watson, C.: Serum calcium, serum gastrin, and gastric acid secretion before and after parathyroidectomy for hyperparathyroidism. Surgery, *75*:841, 1974.
45. Thompson, J. C., Reeder, D. D., and Bunchman, H. H.: Clinical role of serum gastrin measurements in the Zollinger-Ellison syndrome. Amer. J. Surg., *124*:250, 1972.
46. Thompson, J. C., Reeder, D. D., Bunchman, H. H., et al.: Effect of secretin on circulating gastrin. Ann. Surg., *176*:384, 1972.
47. Trudeau, W. L., and McGuigan, J. E.: Effects of calcium on serum gastrin in the Zollinger-Ellison syndrome. New Eng. J. Med., *281*:862, 1969.
48. Trudeau, W. L., and McGuigan, J. E.: Relations between serum gastrin levels and rates of gastric hydrochloric acid secretion. New Eng. J. Med., *284*:408, 1971.
49. Verner, J. V., and Morrison, A. B.: Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Amer. J. Med., *25*:374, 1958.
50. Walsh, J. H.: Use of radioimmunoassay in endocrine GI tumors. Clin. Gastroenterol., *3*:643, 1974.
51. Ward, J., Adesola, A., and Welbourn, R.: The parathyroids, calcium and gastric secretion in man and the dog. Gut, *5*:173, 1964.
52. Wermer, P.: Genetic aspects of adenomatosis of endocrine glands. Amer. J. Med., *16*:363, 1954.
53. Wilson, S. D.: Personal communication.
54. Wilson, S. D.: Ulcerogenic tumors of the pancreas: The Zollinger-Ellison syndrome. *In* Carey, L. C., ed.: The Pancreas. St. Louis, C. V. Mosby Co., 1973, p. 295.

55. Wilson, S. D., Schulte, W. J., and Meade, R. C.: Longevity studies following total gastrectomy in children with the Zollinger-Ellison syndrome. Arch. Surg., *103*:108, 1971.
56. Winship, D. H., and Ellison, E. H.: Variability of gastric secretion in patients with and without the Zollinger-Ellison syndrome. Lancet, *1*:1128, 1967.
57. Yalow, R. S., and Berson, S. A.: Radioimmunoassay of gastrin. Gastroenterology, *58*:1, 1970.
58. Zollinger, R. M., and Ellison, E. H.: Primary peptic ulceration of the jejunum associated with islet-cell tumors of the pancreas. Ann. Surg., *142*:709, 1955.
59. Zollinger, R. M., and Coleman, D. W.: The Influence of Pancreatic Tumors on the Stomach. Springfield, Illinois, Charles C Thomas, 1974.

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Acute and Chronic Pancreatitis

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ACUTE PANCREATITIS

Acute inflammation of the pancreas is an illness with a broad spectrum of severity. It varies from a very mild condition which responds to treatment quickly, to a devastating illness that is nearly totally refractory to all treatment and affects multiple organ systems. Several questions of clinical importance are related to the spectrum of pancreatitis. Does all acute pancreatitis begin as the mild edematous form? Does edematous pancreatitis progress to hemorrhagic pancreatitis? Can treatment of mild pancreatitis prevent its progression to a more severe form of the illness? The answers to these questions are unknown. In some patients the mild form of the disease seems to precede the severe form, suggesting a progression. In other instances the disease seems to begin as hemorrhagic pancreatitis. The safest course of action with regard to treatment is to assume that each case of pancreatitis will progress to the hemorrhagic form and to treat the patient as vigorously as possible.

Etiology

Little is known concerning the specific mechanism of the cause of acute pancreatitis. Alcoholism, biliary tract disease, hyperparathyroidism, hyperlipidemia, heredity, trauma, viral infections, certain drugs, and scorpion stings are all conditions known to be associated with pancreatitis.[2, 6, 31, 46, 49, 55] As more associations are drawn, fewer and fewer cases are relegated to the category of idiopathic pancreatitis.[38] In most large series either alcoholism or biliary tract disease is associated in about 75 per cent of cases.[42, 56]

Biliary Tract Pancreatitis. Occasionally a gallstone impacted in the distal common duct obstructing the pancreatic ductal orifice will produce pancreatitis. More often no common duct calculus is found. Recently Acosta and Ledesma[1] strained the feces in 36 patients with

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acute pancreatitis, and gallstones and found gallstones in the stool of 34, suggesting that stones have passed through the biliary tree.

This interesting observation supports the classic hypothesis that gallstones in the common duct are related to pancreatitis. It has been disturbing to note that patients with pancreatitis and gallstones are not found to have common duct calculi with any greater frequency than patients with gallstones who have never had pancreatitis. The finding of stones in the stool suggest that the stones have passed.

In reviewing operative cholangiograms done on patients operated upon for gallstones and pancreatitis we found 7 of 9 (78 per cent) to show reflux into the pancreatic duct while only 4 of 11 (36 per cent) not having previously had pancreatitis showed pancreatic duct reflex.

A recent observation relating to infection has been of interest.[3] While normal bile entering the pancreatic duct at physiologic pressure does not appear to be toxic, unconjugated bile salts are quite irritating to the pancreas. Certain bacteria (Bacteroides, Streptococcus, and Clostridia) have the capacity to deconjugate bile salts. If the bile of patients with pancreatitis is infected with one of these organisms then the unconjugated bile salts may be responsible for the pancreatic inflammation. The clinical importance of this observation is not known.

Of interest is the observation that acute pancreatitis related to calculous disease of the biliary tract tends to be more lethal than acute pancreatitis secondary to alcohol abuse.[42] The alcoholic however is much more likely to have chronic pancreatitis. While chronic calcific pancreatitis infrequently results from pancreatitis associated with gallstones.

ALCOHOLIC PANCREATITIS. There are numerous theories concerning alcoholism and pancreatitis. It was previously believed that alcohol given intravenously had no effect on the pancreas. Now it appears that pancreatic function is impaired by elevation of the blood alcohol.[37, 39, 51]

Alcohol given enterically stimulates gastric acid production which in turn stimulates the pancreas. One possibility is that the duodenal wall becomes inflamed from the excessive ingestion of alcohol.[47] The inflammation produces edema and partial obstruction at the papilla of Vater. The partial obstruction, coupled with continued pancreatic stimulation, causes pancreatitis. The specific mechanism where by alcohol ingestion causes a pancreatitis remains unknown.

HYPERLIPIDEMIA. It has long been recognized that hyperlipidemia is related to acute pancreatitis. Figure 1 is a photograph of the lactescent serum of a young woman with pancreatitis.

The relationship is still uncertain. The question is whether pancreatitis produces abnormality in serum lipids or certain blood lipid abnormalities predispose to pancreatitis. Most of the patients with hyperlipidemia and pancreatitis have been Frederickson Class IV.[10, 23] It appears that the frequency of their attacks may be lessened by restriction of fat intake. Recently oral contraceptives have been incriminated in pancreatitis with hyperlipidemia.[16]

Regarding other etiologic factors, very little is known concerning the mechanism of initiation of pancreatic inflammation.

Figure 1. The lactescent serum of a young woman with pancreatitis.

Diagnosis

The diagnosis of acute pancreatitis may be exceedingly difficult. Accurate establishment of the diagnosis is urgent since delay in therapy seems to worsen the ultimate prognosis. The key to the diagnosis lies in a high index of suspicion. The classic symptoms are epigastric pain radiating to the back associated with nausea and vomiting. While the pain is typically epigastric, the pain of pancreatitis may be perceived anywhere in the abdomen and the disease may mimic any intra-abdominal problem. The onset of pain is usually gradual and less abrupt than the onset of pain following perforation of an ulcer. As time passes, the pain increases from that of vague epigastric fullness to severe incapacitating and unrelenting pain. The patient is likely to be restless in an attempt to gain relief, in contrast to the patient with a perforated viscus who tends to lie quietly. When compared to the pain of intestinal or ureteral obstruction the pain of pancreatitis does not have the same crampy element but tends to be more constant.

The physical findings are rather pedestrian. Noteworthy is the observation that upon examining the abdomen one finds less tenderness, rigidity, and guarding than might be expected for the amount of pain which the patient is experiencing. Tenderness is usually present in the epigastrium but rigidity is often absent. Bowel sounds are diminished

and gastric dilatation may be present as a consequence of duodenal atony. The electrocardiogram may suggest myocardial infarction.[13] Within 24 to 48 hours of onset, patients with hemorrhagic pancreatitis may develop discoloration in the flanks (Grey-Turner's sign). While unusual, tetany with or without carpal-pedal spasm may evolve secondary to hypocalcemia. A poorly understood phenomenon of severe pancreatitis is the psychic disturbance. There is histologic evidence of brain injury but its cause is poorly understood. The psychosis is often severe, with varying levels of consciousness, restlessness, hallucinations, and coarse tremor. The development of these findings is ominous and associated with high mortality.

Serum amylase remains the single most important test in determining the presence of acute pancreatitis. While it is true the blood amylase level may be elevated in many conditions other than pancreatitis, an elevated serum amylase with the clinical findings to suggest pancreatitis establish the diagnosis until an alternative is proven. Processes which may cause hyperamylasemia include cholecystitis, perforated duodenal ulcer, intestinal obstruction, pyelonephritis, ruptured ectopic pregnancy, and salivary gland pathology. Amylase levels in the blood may be unexpectedly low if the pancreas is so severely damaged that amylase is not released. A more frequent cause of a false negative amylase level in pancreatitis occurs when sampling is delayed. Elevation of serum triglycerides have also been noted to cause false negative amylase findings.[19] Blood amylase peaks in the first 24 to 36 hours following the onset of the pancreatic inflammation and may have returned to normal in 48 hours. Urinary amylase tends to rise more slowly and remain elevated for a longer time.[9] In rare instances amylase may be bound to protein, resulting in elevated blood amylase with normal urine values. The condition is called macroamylasemia.[5]

Serum lipase is generally elevated in acute pancreatitis and tends to rise later than amylase but remains elevated longer. A recent report suggests that lipase is no more helpful than amylase measurement in establishing the diagnosis but the two tests improve diagnostic accuracy when combined.[35]

Methemoglobin levels are often elevated in acute hemorrhagic pancreatitis but are rather nonspecific.[20]

Non-Operative Treatment

The treatment of acute pancreatitis is aimed at (1) stopping the progress of the illness, (2) treating the hemodynamic abnormality associated with the illness, (3) treating the systemic complications, and (4) treating the local complications.

Nasogastric suction and cessation of oral intake are fundamental in treating pancreatitis, although a recent report questions the use of nasogastric suction.[34] The role of anticholinergics remains controversial but most prefer not to use them. Pain should be relieved with meperidine or codeine in the smallest possible dose for the desired effect. Splanchnic block is often quite effective, does not produce increased intraductal pressure, and may allow the total avoidance of narcotics.

The use of antibiotics remains controversial. While the incidence of pancreatic abscess following acute pancreatitis is low (5 to 10 per cent), the incidence of infectious complications is high (30 per cent). The most common organism is E. coli. When pancreatic abscess does occur the mortality is very high. Mortality in pancreatic abscess treated nonsurgically is 100 per cent, while 37 per cent of those undergoing surgical draining will die. Prevention of septic complications is a desirable goal, and cephalothin, 1 gm every 6 hours intravenously, is preferred.

In the early stages (first 4 days) the cause of death is usually shock. The loss of plasma volume and then whole blood may be severe. Early vigorous intravenous fluid administration is of critical importance, and monitoring of hematocrit is helpful. If hematocrit is rising in the first 24 to 48 hours, volume replacement has been inadequate. Central venous pressure monitoring along with urinary output measurement is also helpful. The central venous pressure should be kept 5 to 10 cm of water above baseline, and urinary output at 50 to 100 cc per hr. Solutions containing glucose should be avoided since the patient with acute pancreatitis is often hyperglycemic. Balanced electrolyte solution (Ringer's lactate) in conjunction with 1000 to 2000 cc of protein-containing solution (5 per cent albumin) are preferred. There is some evidence that low molecular weight Dextran may be advantageous. No more than 500 to 1000 cc should be given in a 24 hour period. After 48 hours the hematocrit may fall sharply, suggesting whole blood loss and at that time whole blood may be required. Hypotension greatly increases the mortality of acute pancreatitis. The hypotension, when it occurs in the first 48 hours, is a reflection of inadequate volume replacement. There is no place for vasopressor drugs early in the course of acute pancreatitis. Agents such as norepinephrine and metaraminol worsen the metabolic acidosis in the hypotensive hypovolemic patient and increase the risk of renal failure as well as increasing the mortality. Glucagon has been suggested to be beneficial but recent studies are discouraging.[14, 22, 32, 54]

While treating the hypovolemia of acute pancreatitis one must not forget the metabolic abnormalities commonly associated with the disease. Hyperglycemia often occurs and may produce serious hyperosmolar states. This situation is accentuated if volume replacement is inadequate. Blood sugar should be monitored at least every 4 hours and intravenous insulin given to keep blood sugar levels under 200 mg per 100 ml.

Metabolic acidosis is often associated with acute pancreatitis. It is usually secondary to hypovolemia and impaired cellular perfusion. Occasionally the acidosis may be worsened by the diabetic state present during the acute episode. In general the acidosis is best treated with adequate volume replacement. If the metabolic acidosis persists after volume replacement is adequate, an alkalinizing solution is required. Sodium bicarbonate may be given in aliquots of 50 cc. until the base deficit is corrected.

Hypocalcemia is a frequent sequel to acute pancreatitis. More than any of the other associated abnormalities the magnitude in the fall in serum calcium is related to severity of the pancreatitis. The mechanism

of the fall in serum calcium is not well explained. As lipase escapes from the inflamed pancreas the neutral fat in the mesentery and omentum is converted into free fatty acid. The free acid combines with calcium and calcium salts (soaps) are formed, binding the calcium. Ordinarily a fall in calcium is corrected by mobilization of calcium from the skeletal reserves. Palayon has suggested that in pancreatitis hypocalcemia is not corrected because skeletal calcium release is inhibited.[40] As a mechanism he proposed that glucagon is released from the inflamed pancreas and stimulates the release of thyrocalcitonin which in turn blocks skeletal calcium mobilization. The combination of calcium binding and inhibition of calcium release from bone could explain the hypocalcemia. While this hypothesis is interesting and plausible, it remains to be proven conclusively. Generally the fall in serum calcium does not produce clinical findings and is not of sufficient magnitude to interfere with clotting, cardiac function, or muscle contractility. Calcium gluconate, 1 gm every 8 hours, may be given intravenously if calcium levels fall to a point low enough to produce symptoms. It is generally reported that serum calcium levels below 7 mg per 100 ml portend a fatal outcome in acute pancreatitis. While this relationship is generally dependable there is no evidence that calcium replacement in a patient without symptoms of hypocalcemia serves to diminish the mortality of the pancreatitis.

In recent years there has developed an increasing awareness of the pulmonary complications of acute pancreatitis.[26, 41] It is clear that progressive pulmonary insufficiency is a frequent complication of severe acute pancreatitis. The frequent occurrence of pleural effusion has been long recognized but the fatal pulmonary failure has just recently been described. The cause of the lung failure is unclear. The treatment consists of monitoring arterial pO_2 and obtaining serial x-ray films. When progressive pulmonary dysfunction is perceived, treatment should be instituted with diuretics, fluid restriction, antibiotics, and ventilatory support. Thoracentesis may prove helpful if pleural effusion is present.

Renal failure is an ominous complication of acute pancreatitis. The onset of renal dysfunction is related to inadequate recognition of the need for volume replacement. Whether or not there is specific alteration in renal blood flow, blood flow distribution, or renal function as a result of pancreatitis is not clear. Volume replacement will usually correct the oliguria of acute pancreatitis. Only after volume replacement is adequate as determined by central venous pressure and hematocrit should a diuretic be given.

The initial oliguria of acute pancreatitis is related to plasma volume loss. After 48 to 72 hours hematocrit usually begins to fall. This is true only in severe pancreatitis. The development of a Grey-Turner sign is evidence of retroperitoneal hemorrhage. There is some suggestion that elastase released from the inflamed pancreas digests the elastic layer of arterial walls, resulting in hemorrhage.[4] We have recently seen a patient with splenic artery pseudoaneurysm following a bout of severe pancreatitis. In general the falling hematocrit may be treated adequately with blood replacement. Occasionally the bleeding will be severe enough to require operative treatment.

Operative Treatment

There is considerable disagreement concerning the operative treatment of acute pancreatitis.[33, 53] The issue is two-fold. Is laparotomy justified in acute pancreatitis and if it is what should be done?

There is only one reason to consider operative treatment during an attack of acute pancreatitis and that is when adequate non-operative therapy is failing. A major consideration is the accuracy of the diagnosis. The discovering of a correctable condition such as strangulated intestine or a perforated ulcer at autopsy in a patient treated for pancreatitis is unforgivable. When all the measures available for treating acute pancreatitis have been employed and the patient fails to improve, the diagnosis should be questioned and laparotomy performed.

If pancreatitis is not present then the alternate condition may be treated. If pancreatitis is present certain measures may be of benefit. If the gallbladder is tense it should be emptied by needle aspiration. If stones are present a cholangiogram may be done by injecting contrast material into the ampulla of the gallbladder with an atraumatic vascular clamp placed across the distal portion of the organ forcing the dye into the ductal system. If common duct patency can be established nothing more need be done. If a stone is seen impacted in the distal common duct it should be removed. If conditions do not permit its removal a second less desirable alternative is cholecystoduodenostomy.

A gastrostomy may be beneficial to obviate the need for nasogastric suction.

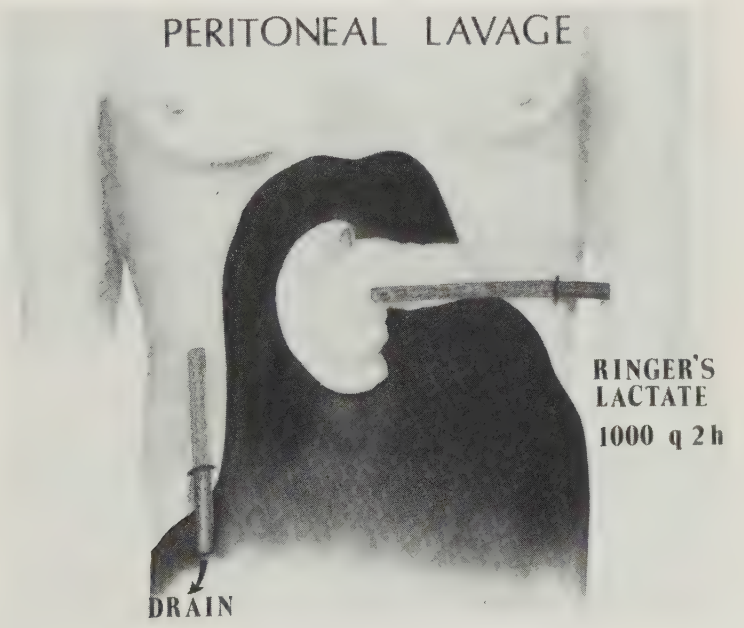

Figure 2. Peritoneal lavage.

A catheter with multiple holes should be placed anterior to the pancreas from a left upper quadrant stab wound. A second catheter should be placed in the right paracolic gutter through a right lower quadrant stab wound (Fig. 2). All easily removable necrotic material should be removed. The abdomen is closed and peritoneal lavage begun with 1000 cc of Ringer's lactate infused rapidly into the peripancreatic catheter. After 1 hour the right lower quadrant tube is opened and the fluid evacuated by gravity drainage. If more fluid is removed than was introduced, then that volume is replaced with intravenous fluid. There is experimental evidence to suggest this approach and we have had considerable encouragement from its clinical application in four cases.[11, 43]

A second question concerns the operative treatment of a patient who has had acute pancreatitis and recovered. A concerted effort should be made to find a cause for the pancreatitis. If it can be determined that alcoholism, lipid abnormality, parathyroidism, and drug reaction are not at fault and the patient has a second documented attack of pancreatitis, cholecystectomy should be performed.[18] This is proper even when gallbladder x-rays are normal. In addition to cholecystectomy, operative cholangiography and biliary manometrics should be performed. If ductal hypertension is present (pressure over 20 cm H_2O) sphincteroplasty should be considered along with transductal pancreatography.[28] While patients fulfilling these criteria are few, most will have small undetectable gallstones and will be relieved of further pancreatitis by cholecystectomy.

CHRONIC PANCREATITIS

As previously stated chronic pancreatitis and specifically calcific pancreatitis are usually secondary to chronic alcoholism.[45, 48] The prognosis of the illness is greatly affected by the continuing alcoholism and early death is associated with the complications of alcoholism. While decreasing alcohol intake may lessen the pain, the pancreatic dysfunction may be progressive.

Gallstones, hyperparathyroidism, and hyperlipidemia are occasionally associated with true chronic pancreatitis. In contrast to the alcoholic, correcting the underlying problem will generally result in amelioration of the pancreatitis in patients with these conditions. If, however, the pancreas has become sclerotic and calcified then it is unlikely that the process can be reversed.[21]

Diagnosis

It is likely that the pathologic process of chronic pancreatitis is well established before the first attack of pain.[27] The pain begins in the epigastrium and typically radiates to the back. Most often its onset is several years after the patient has become an alcoholic. Once there has been one episode of pain the patient may or may not experience subsequent episodes. Generally, repeated bouts of pain will occur with repeated drinking, but each alcoholic indiscretion will not result in ab-

dominal pain. In some patients the episodes of pain will subside spontaneously even though alcoholism and pancreatic injury persist. In others the pain will become more frequent and ultimately result in a high incidence of drug addiction. The major complaint is abdominal pain, as described, with associated nausea and vomiting. As the process continues and pancreatic insufficiency develops, steatorrhea[29] and weight loss are expected. Complications of chronic pancreatitis include pseudocyst formation, diabetes, and less commonly pancreatic ascites, jaundice, splenic vein thrombosis, and portal hypertension.[36, 50]

The physical findings of chronic pancreatitis are no more specific than the historical findings. Most often the only obvious change in the patient is weight loss. There may be mild to moderate tenderness in the epigastrium. The development of a pseudocyst will result in an abdominal mass, the location of which is quite variable. While not common, we have seen several patients with chronic skin changes on the upper abdomen secondary to the long term use of hot water bottles and heating pads.

The x-ray finding of chronic pancreatitis which is diagnostic is the presence of calcium deposits within the gland. About 1 patient in 5 will show changes in the duodenum which resemble those seen with ulcer disease. In general, the small bowel is normal radiographically. In the presence of clinical malabsorption a normal small bowel pattern suggests pancreatitis as the cause of the malabsorption. Arteriography has proven disappointing as a diagnostic tool in pancreatitis.

Laboratory findings supporting the diagnosis are variable. Serum enzymes (amylase and lipase) are usually elevated early in the development of pancreatitis but, as pancreatic destruction progresses, return to normal. Diabetes or abnormal glucose tolerance can be expected in a substantial number of cases. As exocrine function deteriorates, malabsorption from enzyme deficiency develops.

The development of specific tests of pancreatic function has been helpful.[8] Table 1 shows the results of secretin tests from a group of 60 patients from the Gastrointestinal Laboratory at Presbyterian-University Hospital in Pittsburgh. In the patients with proven chronic pancreatitis the average volume of secretin is maintained at normal values (2.0 ml per kg) while the average maximum bicarbonate secretin is depressed to 50 mEq per liter (normal 90 mEq per liter).

Table 1. *Results of Secretin Tests in 60 Patients*

	VOLUME (ml/kg)	HCO_3 (mEq/liter)
Normal	2.0	Max. 90
Pancreatic cancer	0.9	53
Pancreatitis	2.06	50.3
Other*	2.8	95

*Patients with neither pancreatic cancer nor pancreatitis but a variety of gastrointestinal complaints.

Treatment

Once the diagnosis of chronic pancreatitis has been established a plan of treatment should be formulated.[45, 52] Dixon has advocated operative treatment early in the course of the illness and after the diagnosis is certain.[17] From a clinical view point this would mean two or three episodes of recurrent pancreatitis. If no underlying cause for the pancreatitis can be determined, this is clearly the proper approach and most patients will be found to have an abnormality in their biliary tree or pancreatic ductal anatomy. If there is an associated etiologic problem such as hyperparathyroidism or hyperlipemia, initial treatment should be directed toward that abnormality.

The most difficult decision concerns the alcoholic. Clearly the most important aspect in treating alcoholic pancreatitis is the treatment of the alcoholism. Operative procedures on the alcoholic with chronic pancreatitis generally offer little except in relief of pain. If then the disease has not progressed to the point where pain is the major factor, little gain can be expected.

Operative Procedure

The surgical approach to chronic pancreatitis must be planned preoperatively. After exposing the pancreas to determine the extent of disease the anterior superior surface is palpated for the presence of a dilated pancreatic duct. If a duct can be felt then a small (20 gauge) needle is introduced and pancreatic juice aspirated. Two or 3 cc of 50 per cent contrast material is injected, the needle removed, and an x-ray taken. If a dilated duct is not palpable then a pancreaticogram must be obtained by an alternative route. Two possibilities exist. The first is mentioned to condemn it, and that is amputation of the tail of the gland and retrograde ductal injection. This approach is unnecessarily complicated and sacrifices pancreatic tissue which may be important to the patient. The transduodenal approach is preferred. The distal descending duodenum is opened after extensive mobilization of the duodenum and the head of the pancreas. The papilla of Vater is located and a small (No. 10 French) silk woven catheter is introduced into the common duct in a retrograde fashion. A plastic catheter (P.E. 190) is introduced adjacent to the catheter in the common duct and will often enter the pancreatic duct. If it does not, a sphincteroplasty is performed and the pancreatic duct orifice cannulated under direct vision. Choledochoduodenostomy has been suggested as an alternative to sphincteroplasty but does not allow the pancreaticogram.[30] The duct is cannulated, 2 to 5 cc of contrast are injected, and an x-ray film is taken. Enlargement of the pancreatic ductal orifice is accomplished in a manner similar to that used for the sphincteroplasty on the common duct. If a stricture of the pancreatic duct within 4 cm of the ductal orifice is seen, it can be dilated with a small metal dilator or a silk woven catheter. If multiple strictures with dilated ducts between are seen, the longitudinal incision is made through the pancreatic duct and a pancreaticojejunostomy, Roux-en-Y, is constructed.[15, 24, 44] If only the distal pancreas is diseased

then a distal pancreatectomy is performed. Care must be taken to insure that coexisting pseudocysts are drained.

If there is no ductal dilatation, two courses of action are available. When the pancreas is severely diseased, the pain is intense, and exocrine or endocrine insufficiency is established, 95 per cent pancreatectomy will relieve the pain. If the disease has not progressed to that point then nothing beyond assuring ductal patency need be done at this time, but it is likely that a subsequent procedure will be required. Some have found pancreaticoduodenectomy helpful but there is not uniform agreement concerning its application in nonmalignant pancreatic disease.[25]

If sphincteroplasty is done then cholecystectomy should also be performed. Section or removal of the celiac ganglion along with the splanchnic nerves has been used by some with varying degrees of success in relieving pain. These procedures should be done as a part of ductal decompression and not relied upon as the primary procedure for relief of pain.

In general, recurrent pancreatitis associated with biliary tract disease is curable by correcting the biliary tract disorder. Chronic pancreatitis associated with all other conditions is best treated by correcting the associated disease. Once severe pain is established, procedures directed at relieving ductal obstruction if it exists will control pain in 60 to 80 per cent. If the pancreas is destroyed the extensive pancreatectomy is the treatment of choice and will relieve pain in about 70 per cent.

PSEUDOCYST AND ABSCESS

Pseudocyst of the pancreas may follow either acute or chronic pancreatitis. It is generally held that irritating substances exude from the inflamed surface of the pancreas. In an attempt to contain the inflammatory process, surrounding organs and tissues form a capsule. The process may develop rapidly and be obvious within 72 hours of the onset of acute pancreatitis. In other instances the process may evolve slowly over several days or weeks. In general as the pseudocyst develops it becomes associated with pain, vomiting, and the persistent elevation of serum or urine amylase. Occasionally a pseudocyst in the head of the pancreas will obstruct the common bile duct or the duodenum. The diagnosis is confirmed by the development of a palpable mass or evidence of compression of intra-abdominal organs by a space-occupying lesion. Further confirmation may be obtained by the use of sonography. This technique shows promise in enhancing the diagnostic accuracy in dealing with pseudocysts.

Leukocytosis and fevers are common with pseudocyst development and often make the differential diagnosis between pseudocyst and pancreatic abscess quite difficult.[7] The fever pattern associated with a pseudocyst is usually not the spiking picture seen with abscess and the leukocytosis is usually not as striking. Of greater importance is the observation that patients with pancreatic abscesses are usually much more seriously ill than those with pseudocyst.

The organisms infecting the pancreas are usually coliform, E. coli, Aerobacter, and Klebsiella being the most common. Without surgical drainage the mortality of pancreatic abscess is nearly 100 per cent. With proper treatment about one third of the patients will die.

Pancreatic pseudocysts will occasionally subside spontaneously. If the patient is tolerating the cyst with only mild symptoms and in the absence of systemic toxicity there is no particular urgency to drain the cyst. If on the other hand gastric emptying is impaired, ileus is unrelenting, the cyst is enlarging, or the patient is toxic, drainage is urgent.

The treatment of pancreatic pseudocyst is either internal or external drainage. Internal drainage is preferred where possible. Cystogastrostomy is effective, simple, and safe. The most common complication is hemorrhage, occurring in approximately 10 per cent of the cases. One point to be emphasized is the avoidance of oversewing the edges of the cystogastrostomy and individual suture ligation of bleeding vessels is preferred. When the cyst is not adherent to the stomach or when the anatomy of the cyst does not allow adequate dependent drainage with cystogastrostomy cystojejunostomy Roux-en-Y is necessary. The defunctionalized segment must be at least 40 cm long to prevent reflux of the gastrointestinal contents into the cyst.

External drainage of pseudocysts has been condemned because of the risk of pancreatic fistula. While it is true that a significant number of patients will develop fistulas the vast majority will close spontaneously. When the cyst is thin-walled, the patient is seriously ill, and the cyst is infected, external drainage is preferred.

Irrespective of the type of drainage, all pseudocysts should be biopsied. Occasionally a cystadenoma or cystoadenocarcinoma will be mistaken for a pseudocyst.

REFERENCES

1. Acosta, J. M., and Ledesma, C. L.: Gallstone migration as a cause of acute pancreatitis. New Eng. J. Med., *290*:484, 1974.
2. Appel, M. F.: Hereditary pancreatitis. Arch. Surg., *108*:63, 1974.
3. Banks, P. A.: Acute pancreatitis. Gastroenterology, *61*:382, 1971.
4. Bardenheier, J. A., Quintero, O., and Barner, H. B.: False aneurysm in a pancreatic pseudocyst. Ann. Surg., *172*:53, 1970.
5. Barrows, D., Berk, J. E., and Fridhandler, L.: Macroamylasemia—Survey of prevalence in a mixed population. New Eng. J. Med., *286*:1352, 1972.
6. Bartholomew, C.: Acute scorpion pancreatitis in Trinidad. Brit. Med. J., *1*:666, 1970.
7. Bolooki, H., Jaffe, B., and Gliedman, M. L.: Pancreatic abscesses and lesser omental sac collections. Surg. Gynec. Obstet., *126*:1301, 1968.
8. Brooks, F. P.: Testing pancreatic function. New Eng. J. Med., *286*:300, 1972.
9. Calkins, W. G.: A study of urinary amylase excretion in patients with acute pancreatitis. Amer. J. Gastroenterol., *49*:415, 1968.
10. Cameron, J. L., Crisler, C., Margolis, S., et al.: Acute pancreatitis with hyperlipemia. Surgery, *70*:53, July 1971.
11. Carey, L. C.: Use of peritoneal lavage in experimental pancreatitis. Wisc. Med. J., *64*:465, 1965.
12. Cassim, M. M., and Allardyce, D. B.: Pancreatic secretion in response to jejunal feeding of elemental diet. Ann. Surg., *180*:228, August 1974.
13. Cohen, M. H., Rotsztain, A., Bowen, P. J., et al.: Electrocardiographic changes in acute pancreatitis resembling acute myocardial infarction. Amer. Heart J., *82*:672, 1971.

14. Condon, R. E., Woods, J. H., Poulin, T. L., et al.: Experimental pancreatitis treated with glucagon or lactated Ringer solution. Arch. Surg., *109*:154, August 1974.
15. Cox, W. D., and Gillespy, W. J.: Longitudinal pancreaticojejunostomy in alcoholic pancreatitis. Arch. Surg., *94*:469, 1967.
16. Davidoff, F., Tishler, S., and Rosoff, C.: Marked hyperlipidemia and pancreatitis associated with oral contraceptive therapy. New Eng. J. Med., *289*:552, 1973.
17. Dixon, J. A., and Engler, E.: Growing role of early surgery in chronic pancreatitis: A practical clinical approach. Gastroenterology, *61*:375, 1971.
18. Dixon, J. A., and Hillam, J. D.: Surgical treatment of biliary tract disease associated with acute pancreatitis. Amer. J. Surg., *120*:371, 1970.
19. Fallat, R. W., Vester, J. W., and Glueck, C. J.: Suppression of amylase activity by hypertriglyceridemia. J.A.M.A., *225*:1331, 1973.
20. Geokas, M. C., Rinderknecht, H., Walberg, C. B., et al.: Methemalbumin in the diagnosis of acute hemorrhagic pancreatitis. Ann. Intern. Med., *81*:483, 1974.
21. George, P. K., Banks, P. A., Pai, K. N., et al.: Exocrine pancreatic function in calcific pancreatitis in India. Gastroenterology, *60*:858, 1971.
22. Glucagon in Treatment of Acute Pancreatitis. Editorial. Brit. Med. J., *1*:503, 1973.
23. Greenberger, N. J.: Pancreatitis and hyperlipemia. New Eng. J. Med., *289*:586, 1973.
24. Griffin, J. M., and Starkloff, G. B.: Surgery of chronic pancreatitis. Amer. J. Surg., *122*:18, 1971.
25. Guillemin, G., Cuilleret, J., Michel, A., et al.: Chronic relapsing pancreatitis: Surgical management including 63 cases of pancreaticoduodenectomy. Amer. J. Surg., *122*:802, 1971.
26. Halmagyi, D. F., Karis, J. H., Stenning, F. G., et al.: Pulmonary hypertension in acute hemorrhagic pancreatitis. Surgery, *76*:637, October, 1974.
27. Howard, J. M., and Nedwich, A.: Correlation of the histologic observations and operative findings in patients with chronic pancreatitis. Surg. Gynec. Obstet., *132*:387, 1971.
28. Jones, S. A., Steedman, R. A., Keller, T. B., et al.: Transduodenal sphincteroplasty (not sphincterotomy) for biliary and pancreatic disease. Amer. J. Surg., *118*:292, 1969.
29. Kalser, M. H., Leite, C. A., and Warren, W. D.: Fat assimilation after massive distal pancreatectomy. New Eng. J. Med., *279*:570, 1968.
30. Keclik, M., Fric, P., Smat, V., and Friedberger, V.: Chronic pancreatitis and choledochoduodenal anastomosis. GUT, *9*:311, 1968.
31. Kelly, T. R.: Relationship of hyperparathyroidism to pancreatitis. Arch. Surg., *97*:267, 1968.
32. Knight, M. J., Condon, J. R., and Smith, R.: Possible use of glucagon in the treatment of pancreatitis. Brit. Med. J., *2*:440, 1971.
33. Lawson, D. W., Daggett, W. M., Civetta, J. M., et al.: Surgical treatment of acute necrotizing pancreatitis. Ann. Surg., *172*:605, 1970.
34. Levant, J. A., Secrist, D. M., Resin, H., et al.: Nasogastric suction in the treatment of alcoholic pancreatitis. J.A.M.A., *229*:51, 1974.
35. Lifton, L. J., Slickers, K. A., Pragay, D. A., et al.: Pancreatitis and lipase. J.A.M.A., *229*:47, 1974.
36. Longstreth, G. F., Newcomer, A. D., and Green, P. A.: Extrahepatic portal hypertension caused by chronic pancreatitis. Ann. Intern. Med., *75*:903, 1971.
37. Lowenfels, A. B., Masih, B., Lee, T. C., et al.: The effect of intravenous alcohol on the pancreas. Arch. Surg., *96*:440, 1968.
38. Moberg, A., Svenhamn, K., and Wagermark, J.: Acute "idiopathic" pancreatitis. Acta Chir. Scand., *134*:369, 1968.
39. Mott, C., Sarles, H., Tiscornia, O., et al.: Inhibitory action of alcohol on human exocrine pancreatic secretion. Amer. J. Dig. Dis., *17*:902, 1972.
40. Paloyan, E., Paloyan, D., and Harper, P. V.: The role of glucagon hypersecretion in the relationship of pancreatitis and hyperparathyroidism. Surgery, *62*:167, 1967.
41. Ranson, J. H., Turner, J. W., Roses, D. F., et al.: Respiratory complications in acute pancreatitis. Ann. Surg., *179*:557, May, 1974.
42. Romer, J. F., and Carey, L. C.: Pancreatitis: A clinical review. Amer. J. Surg., *111*:795, 1966.
43. Rosato, E. F., Mullis, W. F., and Rosato, F. E.: Peritoneal lavage therapy in hemorrhagic pancreatitis. Surgery, *74*:106, July, 1973.
44. Sato, T., Kakizaki, G., Saitoh, Y., et al.: Side to side pancreatico-jejunostomy with caudal pancreatectomy. Arch. Surg., *96*:892, 1968.
45. Sarles, H.: Chronic calcifying pancreatitis—chronic alcoholic pancreatitis. Gastroenterology, *66*:604, 1974.
46. Sarles, H., Sarles, J. C., Camatte, R., et al.: Observations on 205 confirmed cases of acute pancreatitis, recurring pancreatitis and chronic pancreatitis. GUT, *6*:545, 1965.
47. Shapiro, H., Wruble, L. D., and Britt, L. G.: The possible mechanism of alcohol in the production of acute pancreatitis. Surgery, *60*:1108, 1966.

48. Strum, W. B., and Spiro, H. M.: Chronic pancreatitis. Ann. Intern. Med., 74:264, 1971.
49. Ursing, B.: Acute pancreatitis in Coxsackie B infection. Brit. Med. J., 3:524, 1973.
50. Yale, C. E., and Crummy, A. B.: Splenic vein thrombosis and bleeding esophageal varices. J.A.M.A., 217:317, 1971.
51. Valenzuela, J. E., Salinas, J., and Petermann, M.: Effect of ethanol on pancreatic enzyme secretion. Gastroenterology, 67:991, 1974.
52. Warren, K. W., and Mountain, J. C.: Comprehensive management of chronic relapsing pancreatitis. SURG. CLIN. N. AMER., 51:693, 1971.
53. Waterman, N. G., Walsky, R., Kasdan, M. L., et al.: The treatment of acute hemorrhagic pancreatitis by sump drainage. Surg. Gynec. Obstet., 126:963, 1968.
54. Waterworth, M. W., Barbezat, G. O., and Banks, S.: Glucagon in treatment of acute pancreatitis. Lancet, 1:1231, 1974.
55. White, T. T., Morgan, A., and Hopton, D.: Postoperative pancreatitis. Amer. J. Surg., 120:132, 1970.
56. White, T. T., Murat, J., and Morgan, A.: Pancreatitis: Review of 733 cases of pancreatitis in three Seattle hospitals. Northwest Med., 67:374, 1968.

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Pancreatic Pseudocysts

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Most pseudocysts have a number of features in common despite the widely different histories preceding their appearance. Upper abdominal discomfort, anorexia, or postprandial vomiting usually leads to their discovery, but these masses can grow to amazing size without symptoms. Physical examination discloses a mass in only half the patients even though a large one is present, hidden under the rib margins. Other less specific physical signs are epigastric and left costovertebral angle tenderness or elevated lung bases. Sometimes the abdomen will show only a very prominent transmitted aortic pulsation or an audible bruit.

An upper gastrointestinal series is the mainstay of diagnosis and will show the mass displacing the stomach or duodenum in 77[52] to 86 per cent[51] of patients. It may push the stomach or duodenum in a number of different directions (Figure 1). In the remainder of cases the mass is too small or has ruptured, as in pancreatic ascites. Other abdominal x-rays are of ancillary value: An intravenous pyelogram may show downward displacement or distortion of the left kidney. A barium enema may show the transverse colon thinned out and pushed downward by the mass, whereas it will be displaced upward by a lymphoma in the base of the mesentery. Gallbladder x-rays are needed because of the frequent relation of gallstones to the underlying pancreatitis, even in alcoholics. Chest x-ray films show pleural effusion in 20[57] to 35 per cent.[12]

A serum amylase is elevated in only 41[12] to 55 per cent.[3] A much more sensitive test of abnormal amylase activity is the urine amylase output. This is measured in a timed urine specimen and expressed in units per hour to eliminate fluctuations with changing urine concentration. When done in this way the urine amylase output has been elevated in 80 per cent of pseudocysts.[52] This increased output undoubtedly reflects slow absorption of the enzyme through the walls of the cyst. This process is often too slow to elevate serum levels. Urinary amylase values are therefore much more useful in the investigation of any upper abdominal mass. After a pseudocyst is effectively drained both serum and urine amylase promptly returns to normal.[52]

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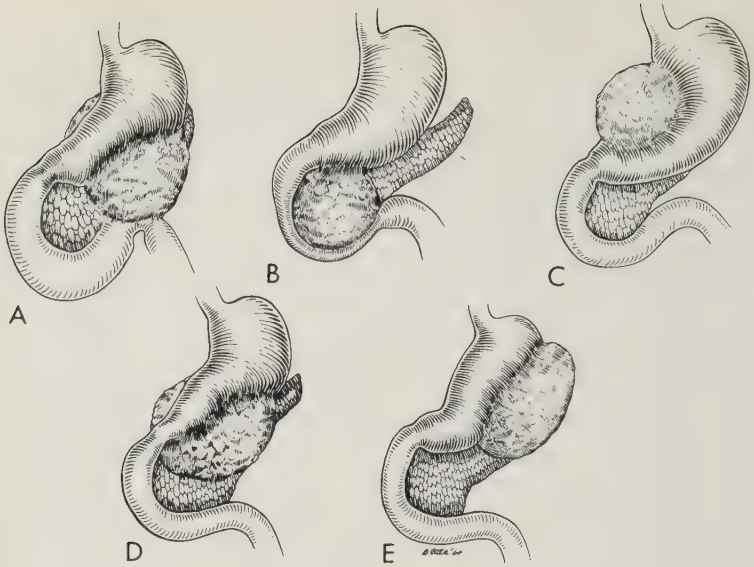

Figure 1. Pseudocysts may: (*A*) push against the ligament of Treitz, obstructing the distal duodenum; (*B*) impress the duodenal C-loop; (*C*) push the stomach to the left or downward, (*D*) upwards, or (*E*) to the right.

Other laboratory abnormalities are much less specific. Leukocytosis occurs in about 50 per cent.[51] Glucose intolerance is demonstrable by either a 2 hour postprandial glucose or a tolerance test in about one half.[12] This reflects the high incidence of chronic and alcoholic pancreatitis preceding the appearance of the pseudocyst.[3]

Pathogenesis

Pseudocysts are distinguished by their content of pancreatic juice. Although this juice is diluted by serum, inflammatory debris, and sometimes frank blood, the cyst fluid contains all the usual pancreatic enzymes in high concentrations. When in doubt about the nature of a mass, it is easy to measure its fluid amylase. This level may range from 3 to 50 times the normal serum values. Lipase, trypsin, chymotrypsin, carboxypeptidase, and other enzymes are all present, as well as bicarbonate. However, this will be neutralized by serous exudate resulting in a normal pH. When not infected, this fluid evokes only a mild inflammatory reaction, producing a shaggy fibrinous exudate on surrounding surfaces. This shell of fibrin is converted in one to several weeks into a tough fibrous capsule which may be softened in places by fat necrosis and inflammatory reaction. There is no central layer of secretory endothelium as in other cysts—hence the name "pseudocyst."

The pancreatic juice in the cyst comes from the acinar cells in the main pancreas. Often this juice comes directly from the major duct, pouring out through a small rupture created by necrosis in the surrounding parenchyma. This communication is hard to find at operation

Figure 2. Ten days after external drainage injection of x-ray contrast into a pseudocyst through the catheter drain shows communication between the cyst and the major pancreatic duct.

but often may be demonstrated later by injection of x-ray contrast material into the tube draining a cyst cavity (Fig. 2).

The localized acinar necrosis may be produced by blunt or penetrating trauma or by a preceding attack of acute pancreatitis. Pseudocysts also appear in the course of chronic relapsing pancreatitis, and in a few cases behind carcinoma in the head of the pancreas. These generally grow more insidiously without a prior acute abdominal episode and have been termed "retention cysts."[33, 54, 55] However, most authors have not made this distinction. In any case, the pathogenesis of these retention cysts appears the same, although the underlying disease in the pancreas is more chronic and persistent.

In the laboratory the pathogenesis of pseudocysts has been elucidated in only a few reports, but these have clarified and confirmed clinical observations. It is possible to produce pseudocysts in dogs if there is first created a walled-off cavity.[56] In human beings this is provided within the capsule of the pancreas or by the lesser peritoneal sac closed at the foramen of Winslow by inflammation. Three elements are then necessary for creation of a typical pseudocyst: (1) ductal rupture communicating with the potential space, (2) an actively secreting pancreas, and (3) interference with normal ductal drainage.[28]

The pressure of pancreatic secretion from the main ductal system forces the pseudocyst to enlarge until it meets counterbalancing resistance. Although human pancreatic secretory pressures have been measured on only a few occasions, these suggest such high levels as 30 cm of water after eating.[60] Further water may be attracted osmotically by the inflammatory protein content of the pseudocyst. Therefore such cysts can grow from the size of a small lime within a thickened pancreatic head[33] to huge masses filling the upper abdomen.

Establishing the Cause

The clinical history obtained when the pseudocyst is recognized can be important in differential diagnosis and treatment. Usually this history will establish one of three situations: (1) the mass has followed shortly after a sudden severe attack of acute pancreatitis, or postoperative pancreatitis; (2) there has been trauma to the upper abdomen, either penetrating or crushing, such as a steering wheel injury; or (3) the onset has been insidious, without any recognizable sudden pancreatic injury. In this group there may be a long history of epigastric symptoms without recent change or of alcoholism or of chronic pancreatitis. There may also be no symptoms of any kind before the pseudocyst appeared.

Recent Acute Pancreatitis Preceding the Mass

If a mass in the pancreas has followed a documented or probable attack of acute pancreatitis it is not necessarily a pseudocyst. There are three likely causes to be differentiated. This mass may be (1) an abscess with infected sloughing pancreas and juice in the lesser sac, (2) a mixture of tremendously edematous and necrotic pancreas with little or no cystic component, or (3) a developing pseudocyst.

It is important to differentiate these three because the subsequent management of each is different. Unfortunately in making this decision, the cause for the acute attack is not of much help. All three lesions can follow any of the known causes for pancreatitis. Postoperative acute pancreatitis, however, is much more likely to be followed by either an abscess or an infected pseudocyst. The most minor contamination at operation grows rapidly in such excellent media as necrotizing pancreatitis, and contamination is greatly increased with the use of postoperative drains.[31]

Differentiating Pancreatic Abscess

A pancreatic abscess presents the most immediate danger to the patient. Characteristically this is heralded by fever and paralytic ileus in a patient who appeared to be recovering from pancreatitis. In uninfected pseudocysts or edematous pancreatitis fever is unusual and ileus clears earlier. White blood cell counts are consistently elevated in abscesses, averaging 18,000, while the other laboratory results are less specific. These reflect the abnormalities expected after severe pancreatitis and in the face of sepsis: depressed hematocrits, low albumin, and sometimes hypocalcemia. There have been elevated bilirubin and transaminase levels in almost half the patients, and retention of urea nitrogen and

creatinine in one third.[31] Plain x-ray films are helpful in that one third show basilar atelectasis, pleural fluid, or diaphragmatic elevation. Most abdominal films show paralytic ileus. Plain films may show extraluminal gas in the lesser sac or the "soap bubble" pattern characteristic of retroperitoneal sepsis. While these signs may localize the process, they are present in no more than 25 per cent of cases. On the other hand an upper gastrointestinal contrast examination will point to the mass in 80 per cent of cases.[31]

When faced with such intra-abdominal sepsis perhaps the most useful laboratory help comes from repeated blood cultures. When positive, these identify the invading organism and its sensitivities. Multiple organisms are found in cultures of the abscess in at least 50 per cent of cases. The varieties are similar to those found elsewhere in the gastrointestinal tract, being more than two thirds coliforms.[31]

Hemorrhage

Primary pancreatic abscesses and secondarily infected pseudocysts act much alike. As a result the abscess may discharge itself into the chest or bronchus, or more commonly into the colon or duodenum. This is not a satisfactory resolution, however, since such erosion is almost always accompanied by a major gastrointestinal hemorrhage requiring emergency operation.

Clotting mechanisms have been found abnormal in a signficant number of patients. Sepsis, shock, and prior hepatic injury contribute to this. Prolonged starvation, nasogastric suction, and potent antibiotics cause hypoprothrombinemia. Since this may be reversible with parenteral vitamin K, prothrombin levels deserve special attention before hemorrhage appears.

Erosions of such major arteries as the splenic, gastroduodenal, or inferior pancreaticoduodenal arteries within these abscesses have been a problem as well. This occurs much more frequently in the presence of sepsis than without it. In a few cases the sudden appearance of a bruit over a pancreatic mass has provided a warning before hemorrhage breaks loose.[22] Once bleeding is active, emergency selective visceral angiography can localize its origin. This may be a stress erosion of adjacent gastroduodenal mucosa, or a major artery within the cyst. Infusion of pitressin through selectively placed angiographic catheters has been successful in mucosal hemorrhage in 65 per cent of cases,[39] but is rarely successful in hemorrhage from a major arterial trunk. Such problems with hemorrhage have complicated pancreatic abscesses in 26 of 63 cases, and led to mortality in 80 per cent. However, aggressive operation has been successful in two separate recent reports. Preoperative angiography led to precise intracystic ligation of one or more major arterial trunks, and this has been combined with suitable drainage for the cyst[44, 61] (Figs. 3 and 4).

Operation for Abscess

Obviously early drainage of pancreatic abscess is highly desirable. Its importance has been emphasized in a recent large series. Among 29

Figure 3. Preoperative angiography during gastrointestinal hemorrhage shows contrast filling a pseudocyst in the head of the pancreas from an eroded inferior pancreatoduodenal artery.

Figure 4. Repeat angiography 24 hours postoperatively by the same catheter as in Figure 3 confirms that ligation has controlled the bleeding.

patients who survived operative drainage of abscesses the interval between onset of symptoms and operation averaged 5.5 days. Among the patients who died despite operation this interval averaged 11.5 days.[31] If antibiotics are to be used postoperatively, they should be started before operation. Their selection should be based on cultures of wounds, drains, or positive blood cultures whenever possible. Where such results are not available two or three agents in high doses should be selected to cover a broad spectrum of gram-negative and anaerobic organisms.

There is no general agreement on the operative approach. For most patients an anterior abdominal exploration seems better than a more limited flank incision. This is because these abscesses are multiple or multiloculated in one third of the cases.[31, 58] For good drainage multiple large sump catheters are necessary. These should be brought out laterally in as dependent a position as possible. Usually they will be needed for more than a week, but they should not be allowed to clog up with fibrin and pancreatic debris. They may be removed, cleaned, replaced, and irrigated with antibiotic solution once tracts are established.

This is not a situation in which to consider internal drainage to the stomach or jejunum, since the walls of the cavity are acutely inflamed. The drainage needs to be as adequate as possible or hemorrhage will follow, and recurrent sepsis is common. A second operation for drainage of a recurrent or overlooked abscess has been required in 30 per cent of cases, but even this has been followed by a successful outcome.[58] Nevertheless, the mortality remains distressingly high, averaging 50 per cent.[8, 31]

Indolent Inflammatory Swelling of the Pancreas

Where spesis is not a threat, time can be taken to differentiate between a pseudocyst and a mass of indolent edema and inflammation following pancreatitis. This lesion has been labelled a "phlegmon" of the pancreas, and is being recognized with increasing frequency.[57] A recent experience with 9 such cases has been reported, including 3 patients who had peroral endoscopic pancreatograms. This examination showed normal duct structure in two patients and minor changes in a third patient whose mass disappeared.[46] Folk and Freeark[17] have coined a graphic name for this condition: "pseudo-pseudocysts."

In thin individuals a tender epigastric mass may be palpable after abdominal distention and peritoneal reaction subside. Fever is rare or low-grade, but leukocytosis is common. The serum and urine amylase values may occasionally remain persistently elevated so that these data cannot be used to distinguish this mass from a pseudocyst.

The frequency with which such masses are recognized in relation to pseudocysts depends on how often an upper gastrointestinal contrast x-ray exam is obtained in subsiding pancreatitis. However, many reported series of pseudocysts have included from 21[52] to 35 per cent[20] of patients who have responded to medical management with complete subsidence in 1 to 3 months. It has seemed very likely that many of these masses were phlegmons rather than true pseudocysts. This is because such indolent edematous pancreatitis has been documented at operation,

followed postoperatively with repeated upper gastrointestinal series, and observed to subside (Figs. 5 and 6). It is also possible that some pseudocysts will spontaneously subside, particularly smaller cysts. However, this fact has not been documented since most cysts found at operation have been treated. Without operation the nature of the mass cannot be truly known.

Operation on phlegmonous pancreatitis is frustrating, since very little of the edematous and necrotic debris can be safely removed. Multiple needle aspirations should be performed to rule out a deep-seated cyst, but these usually locate no more than a few cc of pancreatic juice. Cultures should be obtained and if there is doubt about infection a rapid smear and stain of the exudate should be examined for organisms. If ei-

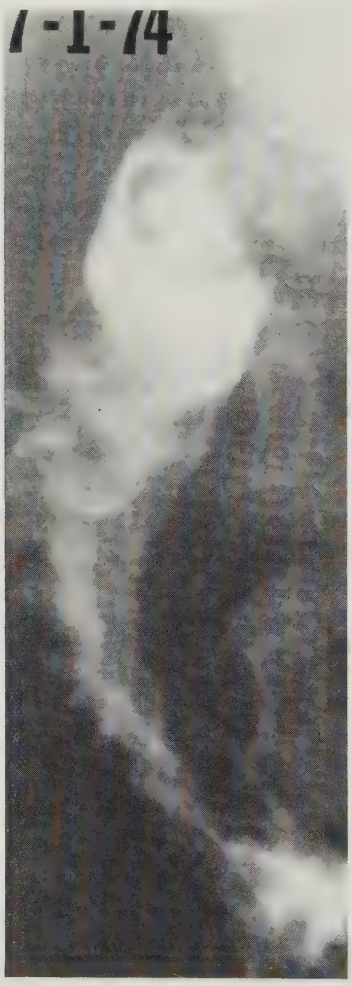

Figure 5. A 54 year old man had fully recovered from an attack of alcoholic pancreatitis when a barium meal suggested a mass in the head of the pancreas impressing the medial side of the duodenal C-loop.

Figure 6. Since the patient shown in Figure 5 was asymptomatic he was followed and re-examined after 6 weeks. The suggestion of a pancreatic mass has disappeared.

ther infection or a small cyst is found, external drainage is important. However, if neither is present the abdomen should be closed without drains since it is important not to introduce infection. Under postoperative treatment for pancreatitis such masses will continue to subside. The patient needs to be followed carefully for several months since in a few cases a pseudocyst will gradually become definite and require another operation.

Among 19 patients operated upon for pseudocyst at the Pittsburgh University Drive Veterans Administration Hospital in the past 5 years, 2 have had phlegmonous pancreatitis. During this same interval 4 additional patients have been followed to full resolution of similar masses without operation. Periods up to 4 months have been required. The decision to avoid operation in the past has been made entirely on clinical

grounds. Generally four elements have been present. (1) The patients have had recent documented acute alcoholic pancreatitis so that a neoplasm was highly unlikely. (2) Other causes for pancreatitis such as gallstones or hypercalcemia have been ruled out. (3) The clinical recovery of the patient progressed satisfactorily without symptoms from the mass. (4) The patient refrained absolutely from further use of alcohol at least during the period of follow-up.

Diagnostic Ultrasound

This problem of differentiating cystic from solid lesions in the pancreas is going to be greatly simplified by diagnostic ultrasound echograms of the upper abdomen. Experience with this new, safe, and noninvasive technique is developing rapidly. Current reports justify placing some confidence in it. Sound waves with frequencies of two and one quarter million cycles per second are reflected from tissue interphases with different acoustical impedances. The echoes may be stored and displayed on a persistence scope and photographed for the record. The picture provides a transverse or a longitudinal cross-section of the abdomen with lines outlining organ and tissue interphases. Normal organs and homogeneous fluid-filled cysts produce few echoes, except from their borders. In contrast, pancreatitis or carcinoma produces many echos, while the normal pancreas cannot usually be outlined (Figs. 7 and 8). This permits differentiation of cystic from solid pancreatic masses with greater confidence than is now available from any other technique, including angiography.

Bradley and Clements have applied diagnostic ultrasound to 19 patients thought to have pancreatic pseudocysts clinically and who subsequently had an operation or autopsy. In 10, pseudocysts were predicted and confirmed by operation. In 9 patients phlegmonous pancreatitis was predicted and this was correct in 8, there being one false-negative report.[9] Stuber, Templeton, and Bishop[49] have reported a diagnostic accuracy of 85 per cent in the pancreas, including a prediction of pancreatic carcinoma in 7 of 8 cases. The technique is equally applicable to intra-abdominal abscesses and hematomas, being correct in 43 out of 50 examinations.[25]

Post-Traumatic Pseudocysts

After trauma to the pancreas a pseudocyst can appear in 1 to 2 weeks, but more often after 2 or 3 months. A collection of pancreatic juice in the lesser sac implies injury to a major pancreatic duct. The history of the injury is helpful in making a judgment about the underlying pancreatic lesion. When there has been a penetrating wound by a knife or bullet, the farther to the right and closer to the duodenum such an injury occurs, the larger is the leak of juice and the more serious will be the problem.[27] When the collection appears early, usually shortly after the removal of drains, risks are increased. Secondary infection, with abscess formation and pancreatic slough is very likely, with its increased risk of serious hemorrhage. Reoperation should be undertaken promptly without waiting for development of a suitable cyst wall. Mul-

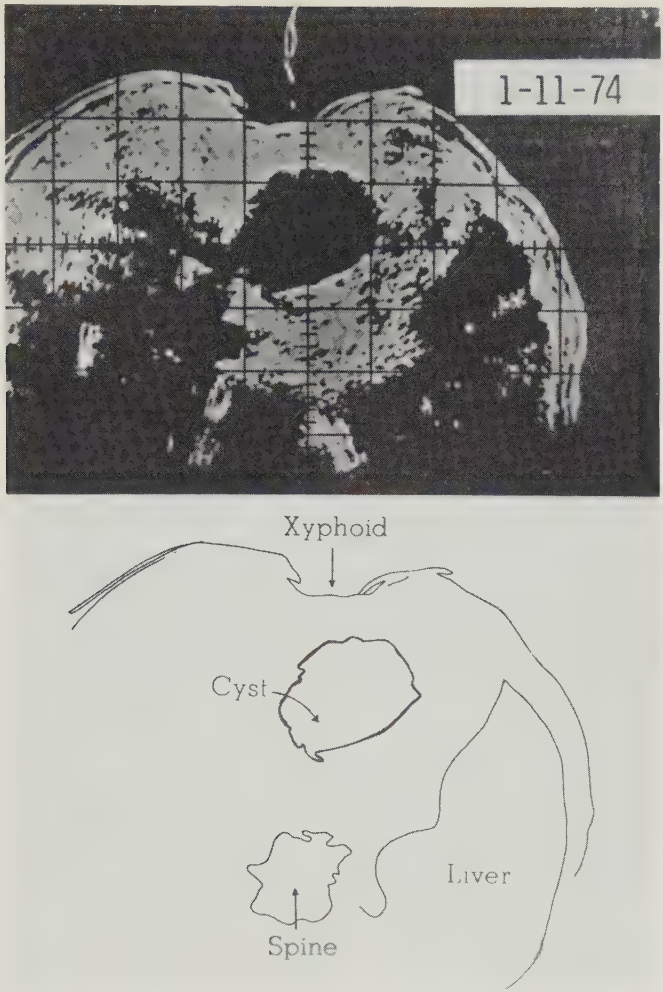

Figure 7. Transverse section of the upper abdomen obtained from B-mode ultrasound echogram in 40 year old man with pseudocyst in the head of the pancreas, later proved by operation.

tiple large sump drainage tubes should be placed very close to the visible pancreatic injury and brought out the flanks in as dependent a position as possible. Sump drains are clearly superior to soft Penrose drains for this purpose. Even at the initial laparotomy for pancreatic trauma, sump drainage combined with hemostasis and debridement has been as effective as caudal resection in preventing future complications.[2]

When the pseudocyst appears later, after full recovery from injury to other adjacent organs, the danger of secondary infection and erosion of vessels is less. The time for an elective operation depends on the urgency of symptoms, but most such cysts will need to be drained. Internal drainage can be considered if the cyst walls are firm and well-formed. However, if other injuries are still a problem, or the cyst has

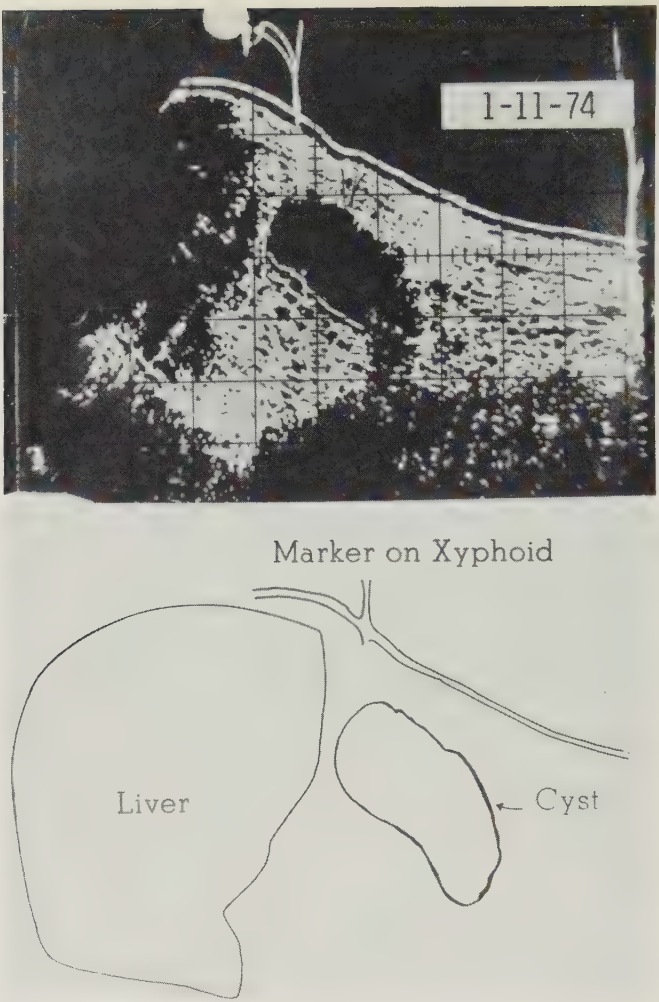

Figure 8. Longitudinal section of upper abdomen in same patient illustrated in Figure 7.

been rapidly enlarging and therefore has delicate walls, then external drainage remains a good choice.

After blunt trauma the situation is somewhat different. An immediate laparotomy may or may not have been performed. If it was, all that may have been seen was a contused organ that appeared to contain a hematoma under its thin capsular membrane. This is usually best left alone, even though a pseudocyst may appear later. In these circumstances the true situation is that the body of the pancreas has been crushed into two parts. This injury takes place directly over the firm vertebral bodies in the midline. Perhaps the transection is a little to the right or the left, depending on the direction of the blow. After the tail of the pancreas resumes active secretion, its juices pour out into the mid-

line hematoma, creating the cyst. This cyst usually grows slowly and may well be suitable for internal drainage. However, collapse of the cyst can leave the divided left half of the pancreas draining poorly through a strictured duct. A new cyst or chronic pancreatitis may then develop. Therefore, when technically feasible, the divided left half of the pancreas ought to be removed in treating this kind of cyst after blunt trauma.

Whenever the surgeon approaches post-traumatic pseudocysts with a plan for internal drainage and then finds that external tube drainage is all that can be done technically, he ought not to feel greatly disappointed. An important fact favors a satisfactory result. The underlying pancreas was very likely normal before the injury. Therefore, the usual functional obstruction in the major ducts distal to the cyst is likely to disappear as inflammation and paralytic ileus clear. While external tube drainage of the cyst will almost certainly lead to a temporary fistula, such a fistula often closes spontaneously after a few weeks (Figs. 9 and 10). If it fails to do so after a reasonable wait, it is usually not difficult to attach a Roux-en-y loop of defunctionalized jejunum to the fibrotic origin of the fistula at the pancreatic surface.

Most pancreatic pseudocysts in growing children are caused by blunt trauma to the abdomen. The results of simple sump tube drainage to the outside have been good, probably because the underlying pancreas has been free of disease or ductal obstruction.[34]

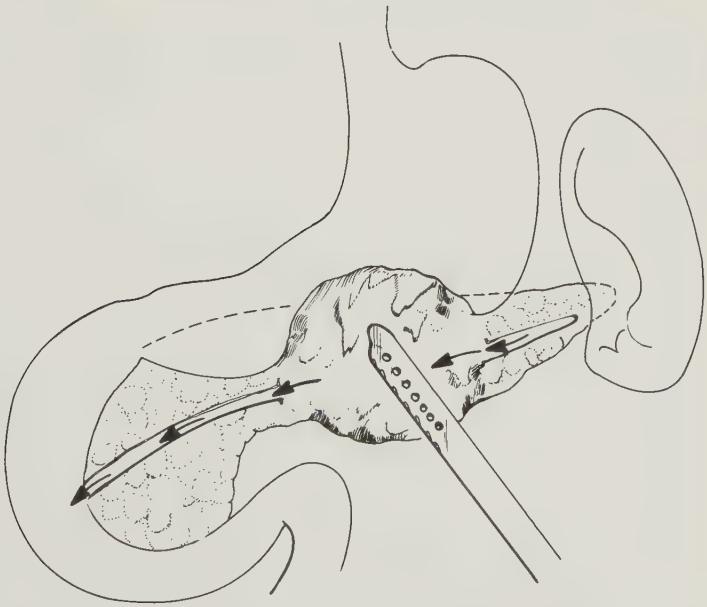

Figure 9. Simple sump tube drainage of a post-traumatic pseudocyst often heals without a fistula because the underlying major pancreatic ducts are not obstructed or diseased.

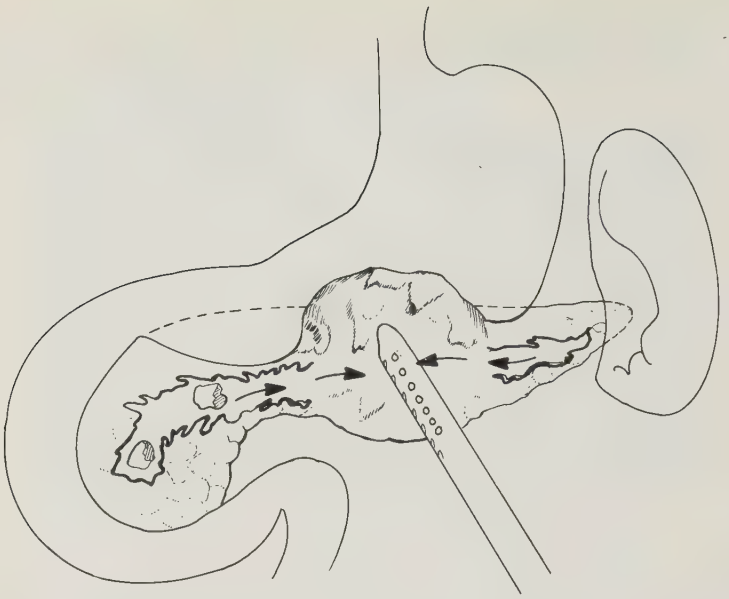

Figure 10. In contrast to the situation in Figure 9, external tube drainage in chronic pancreatitis often leads to a prolonged fistula because the major ductal system is at least partially obstructed.

Pseudocysts After Acute Pancreatitis

A true pseudocyst may appear relatively early in an attack of acute pancreatitis. For treatment of the acute attack, nonoperative measures are the mainstay. Operation is reserved for specific indications related to uncertain diagnosis and acute abscess formation.[4, 16] The pancreas should be kept at rest until the accompanying paralytic ileus has resolved if at all possible. While the patient is improving clinically a persistently elevated serum or urine amylase may be a harbinger of pseudocyst formation, but this alone should not rush an operation.[19] A higher mortality for operations performed too early has been emphasized.[13] The need to allow the wall of the pseudocyst to mature before it can be sutured has also been pointed out.[3, 13, 54] Efforts have been made to measure the actual thickness of the pseudocyst wall before operation by ultrasound but these are not yet successful.[9] Serious problems have been described when attempts are made at internal anastomosis before cyst walls are mature. External drainage should be used in these circumstances.[37]

All these factors indicate delay in operation, but there are also serious hazards in delay. Secondary infection is a distinct possibility, requiring treatment as an abscess. Even without infection, erosion of a major arterial trunk has occurred with hemorrhage into the cyst.[44, 61] Large pseudocysts have ruptured acutely into the free peritoneal cavity. Whereas slow leak and occult rupture lead to pancreatic ascites, sudden

rupture is shocking. This has resulted in mortality in 5 out of 6 cases.[20] When a known cystic mass in the pancreas suddenly disappears and is followed by peritoneal irritation, emergency operation for drainage of the leaking pancreatic juice seems indicated, and has been successful.[41]

The timing of an elective operation for pseudocyst is best dictated by the clinical course of the patient. When the cyst is enlarging rapidly, painful, causing obstruction, or producing fever, operation should proceed without delay. On the other hand, when all symptoms of pancreatitis are clearly receding, and the patient is eating comfortably, a delay to about 6 weeks following pancreatitis seems warranted.[13]

Before operation the cause for the attack of acute pancreatitis should be delineated whenever possible. Hypercalcemia should be ruled out. Hyperlipidemia, drug, familial, and alcoholic pancreatitis should be identified since these must be dealt with postoperatively. It is particularly important to rule out biliary disease by adequate x-rays before operation, even in alcoholics. X-rays are generally more accurate than palpation at operation in an upper abdomen crowded with a mass and edematous with inflammation. When indicated, cholecystectomy with cholangiography can often be performed at the same operation after the cyst is decompressed.[3, 55]

Pseudocysts Complicating Chronic Pancreatitis

The insidious development of a lesser sac mass may be the first sign of pancreatic disease. An accurate history of the quantity of alcohol used each day may be helpful in finding a cause. Many patients will deny any problem with alcohol up to that time. While it has not been possible so far to determine what quantity of alcohol is significant in pancreatic disease, a pattern of daily use is frequently found. Such apparently innocent amounts as 3 or 4 12-ounce bottles of beer a day are often recorded. It is important to recognize, however, that a 12-ounce bottle of beer is roughly equivalent in alcohol content to 2 ounces of 80 proof whiskey and 4 bottles is equal to 10 ounces a day. It is also quite clear that an unexplained pseudocyst is an unequivocal sign of serious pancreatic disease. After it is recognized in a patient using alcohol, any quantity of alcohol thereafter becomes a further pathogenic factor.

When alcohol has been excluded, a search for the other known causes for pancreatitis becomes more important. In only a very few patients will no cause be found. In these patients the differential diagnosis of the mass needs to include a number of other lesions, some of them rare. Lesions which have been found are: (1) aneurysms of the splenic, hepatic, or pancreatoduodenal arteries, or of the aorta if unusually high; (2) neoplasms in the lymphoma group, such as reticulum cell sarcoma, hemangioendothelioma, Hodgkin's disease, and lymphosarcoma; and (3) unusual neoplasms of the pancreas itself such as cystadenoma and cystadenocarcinoma or congenital "bluedomed" or multiloculated cysts.[40] It is also unfortunately true that a pseudocyst may develop behind an adenocarcinoma, obstructing the major ducts,[18] and this can easily go unrecognized even at operation.[10]

In such masses of unknown cause there is an important place for

selective celiac angiography. Aneurysms may be ruled out and malignancies can usually be identified. Since pseudocysts are largely avascular they may also be recognized, but they cannot be differentiated by angiography from edematous pancreatitis. Diagnostic ultrasound will be superior for this purpose. Cystadenomas and cystadenocarcinomas of the pancreas have been diagnosed preoperatively by a mixture of absent vessels in cystic spaces combined with tumor vasculature[1] (Figs. 11 and 12).

OPERATION FOR PSEUDOCYSTS

Operation for pseudocyst is not altogether as safe as it should be for a benign inflammatory disease. While Warren and Badosa report 133 operations with only 4 deaths yielding a mortality of 3.4 per cent[55] and there have been other reports with low mortality,[35] these are exceptional in recent years. A summary of seven other sizable series published since 1968 includes 401 patients undergoing operation with deaths in 42 or 10.4 per cent.[3, 6, 13, 20, 41, 43, 51, 54] The mortality figures ranged from 4 deaths in 64 patients at 6.2 per cent[43] up to 8 deaths in 50 patients or 16 per cent.[51] In many reports mortality seems a little less for internal drainage than for external, but this is no doubt related to the use of external drainage in sepsis, and in the more desperately ill patients. The high risk seems particularly related to the associated liver disease and portal hypertension in alcoholic patients. There is also a tendency to develop peptic ulcer in severe pancreatitis[15] with gastrointestinal hemorrhage whenever stress appears.[30]

With the current operative mortality averaging 10 per cent, it is clear that preoperative evaluation cannot be routine. Liver function needs attention and especially the prothrombin time since preoperative vitamin K may be needed. Plasma albumin may be low and preoperative intravenous albumin may be helpful during operation and for a few days thereafter. Platelet counts are indicated because hypersplenism may be present and easily overlooked. Splenic vein thrombosis complicates pancreatic masses[26] and may contribute to both hypersplenism and venous hypertension, with bleeding at operation. Since the stomach and jejunum may be opened or the cyst infected, preoperative broad spectrum antibiotic prophylaxis should be considered.[36] This is particularly true of the 10 per cent of cases that also present obstructive jaundice.[14]

An upper midline incision provides good exposure if placed high enough, extending above the xyphoid in most cases. The absence of gallstones needs to be confirmed and the head of the pancreas examined to rule out carcinoma. If the cyst is already intimately adherent to the stomach, cystogastrostomy through these adhesions is probably the simplest and best current procedure. However, it is important to make this decision before peeling away any adhesions to the cyst or the mesocolon. It is extremely easy to break into the cystic mass inadvertently, and this rules out the cystogastrostomy. Such holes cannot be closed securely, and would lead to gastric-cyst-peritoneal fistulas. If the

Figure 11. Celiac angiogram shows the pancreatoduodenal artery stretched out and around an avascular space representing a pseudocyst in the head of the pancreas.

Figure 12. Superior mesenteric angiogram shows the inferior pancreatoduodenal artery (arrow) depressed by an avascular pseudocyst.

cyst is not adherent to the stomach or if it is broken into, no effort should be made to suture the capsule to the stomach. Instead, a Roux-en-y 12 inch loop of jejunum should be anastomosed to the opening, or to the most dependent available point for drainage. This is a safer procedure than cystogastrostomy because the jejunal loop is defunctionalized.

Regardless of the route of drainage chosen, the fluid should be cultured, and its amylase concentration determined to confirm its pancreatic source. In addition a biopsy of the cyst wall should be taken to rule out a cystadenoma. These lesions may appear grossly very much like pseudocysts but can be cured only by en bloc resection.[7] In contrast resection is not usually necessary or desirable for benign pseudocysts, and has led to a high mortality.[6]

If a cystogastrostomy seems feasible, the anterior wall of the stomach should be opened directly opposite the point chosen for entering the cyst. The cyst should then be needled through the posterior gastric wall to establish its nature and ensure that it can be entered safely at this point. A relatively large communication admitting several fingers should be made[3, 54] (Fig. 13). Although resection of stomach wall has been advocated,[45] this has not been necessary in my experience. With a large opening the inside of the cyst can be gently explored with fingers and instruments to eliminate occasional loculations. A biopsy of the cyst wall should be easily obtained. Hemostatic sutures should be placed

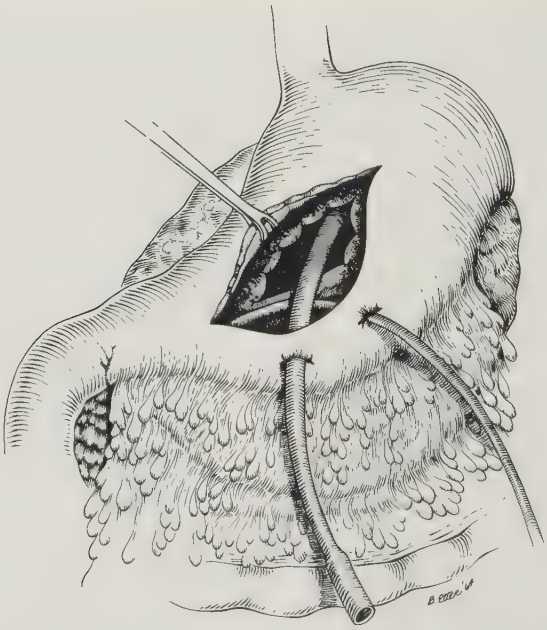

Figure 13. A relatively large opening has been made into a retrogastric pseudocyst through an anterior gastrotomy. A catheter has been threaded through the anterior gastric wall into the depths of the cyst to ensure good drainage as the cyst collapses. A tube gastrostomy has also been placed.

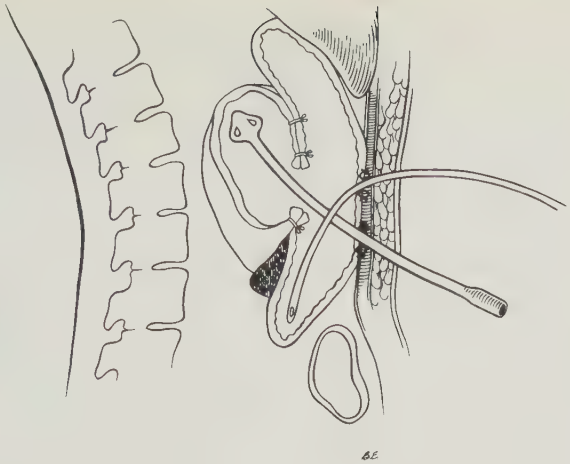

Figure 14. Lateral view of the procedure shown in Figure 13.

around the cystogastrostomy margins. Postoperative gastric bleeding has been attributed to these sutures.[23] However, they have been helpful in my opinion, and do not contribute to postoperative bleeding if a generous opening has been made.

A tube may be threaded from the depths of the cyst, through the stomach, and to the outside to ensure good drainage (Fig. 14). This may be helpful when the cavity is large, tortuous, or multiloculated. The cyst walls rapidly collapse around this tube, and this may be seen by injecting radiopaque dye postoperatively. The tube may be withdrawn in 1 to 2 weeks. The progressive closure of a cystogastrostomy opening has been observed by repeated gastroscopy. Closure took place about 6 weeks after drainage of a very large cyst, with good results.[53] Experience with cyst-duodenostomies for small cysts close to the duodenum has been limited, but has not yielded as good long-term results, probably because the opening must be rather small.[43]

Follow-up has shown relatively good results for internal drainage, with very little difference between cystogastrostomy, cystojejunostomy, and resection. However, recurrent cysts have occurred in 6 per cent[55] to about 15 per cent of cases.[6, 17, 41] This is a considerable improvement over external drainage in which a further operation has been needed in 25 to 40 per cent.[6, 43] Alcoholic patients will continue to have other manifestation of pancreatitis unless alcohol is discontinued,[3] and diabetes has been reported in as many as 40 per cent.[52]

UNUSUAL PRESENTATIONS—OFTEN WITHOUT MASSES

Pseudocysts have presented in an amazing variety of ways both with and without evident masses. In chronic pancreatitis, cysts within the head of the pancreas too small to be recognized by upper gastroin-

testinal series have been found at operation by needle aspiration. Cyst-duodenostomy has relieved this source of abdominal pain.[33] Similar lesions have produced typical obstructive jaundice without any other signs of a pseudocyst. Appropriate operative drainage relieves the problem.[21]

At the opposite end of the pancreas small cysts have invaded the spleen, so that a technetium splenic scan gave the best clue to their presence. These masses could usually be resected with splenectomy.[59] Similar invasion of the left kidney has been the first presenting symptom, so that the diagnosis of intrarenal pseudocyst has been made first by urologists, after intravenous pyelography.[48]

The pressure of pancreatic secretion aided by its potent enzyme content can burrow surprising distances, forming distinct tracts surrounded by fat necrosis, detritus, and woody inflammation. These follow, by chance or proximity, one of three favorite routes: (1) The tract may extend upward through the esophageal hiatus into the posterior mediastinum where a true pseudocyst may develop.[24] This tract can extend further and present as an abscess in the neck.[50] (2) The right lateral lumbar gutter is a second area for tract formation from the head of the pancreas. (3) The left lumbar gutter is involved from the tail. Tracts dissecting downward and laterally on the right have presented as abscesses in the groin[42] or even through the groin into the scrotum.[57]

Cysts may form anywhere along the course of such tracts, and where pressure builds up, adjacent viscera may be eroded. Colonic necrosis has been encountered, often at the hepatic or splenic flexures where the colon is less mobile, resulting in a colopancreatic fistula.[29] This infects the entire cyst or lesser sac with colonic organisms, and can be a disastrous complication of undrained pancreatic juice. Figure 15 shows a barium enema which demonstrated such a communication between the posterior surface of the hepatic flexure and a pseudocyst behind the head of the pancreas. At emergency operation the entire right lumbar gutter was filled with fat necrosis and extensive woody inflammation. This was drained laterally. No effort was made to find or resect the fistula. A by-passing end-to-end ileo–left colostomy was performed. The distal end of the right colon was brought to the outside as an end-colostomy, to ensure complete defunctionalization. The patient had a good recovery.

Chronic or recurrent pleural effusions of pancreatic juice are probably caused by similar burrowing and erosion. The effusions may be bilateral and heavy with plasma proteins or appear hemorrhagic.[32] The process may start with an underlying pseudocyst but discharge of its contents through the esophageal hiatus or an eroded diaphragm into the pleural spaces decompresses the cyst in the lesser sac, leaving a chronic fistula behind. The true nature of the disorder can be identified by a measurement of amylase and protein in the fluid removed at thoracentesis. The simultaneous serum amylase may be normal.

In a few instances these pleural effusions have been successfully treated by tube drainage of the chest and suppression of pancreatic secretion. This requires atropine, acetazolamide (Diamox), and nasogas-

Figure 15. The post-evacuation film in a barium enema shows leak of contrast into a retroperitoneal tract in the right lumbar gutter created by pancreatic juice dissecting downward after a bout of alcoholic pancreatitis.

tric suction, with parenteral nutritional support for a period of 2 to 3 weeks.[5]

The alternative is an abdominal operation. The best current procedure is the drainage of the proximal main pancreatic duct into a Roux-en-y loop of defunctionalized jejunum, as Peustow and Gillesby described for chronic pancreatitis. At operation, access to the main duct may be obtained through even a small pseudocyst, by opening the fistulous tract, or by needling the body of the pancreas.[38] If none of these succeed, then the spleen and pancreatic tail can be resected to permit identification of the main duct in the proximal end of the gland, but this should not often be necessary.

Pancreatic ascites represents a very similar situation, but the true cause for ascites is even more likely to be overlooked. This is because this lesion occurs in middle-aged alcoholic patients who may never have

had an identifiable attack of acute pancreatitis. It is easy to attribute the ascites to alcoholic liver disease which may also be present. However, the finding of high urine amylase output or a modest elevation of serum amylase should raise the suspicion of a pancreatic origin. Confirmation will be obtained by a determination of amylase in ascitic fluid, which will regularly be high. At operation an underlying ruptured pancreatic pseudocyst has been found in two thirds of the cases.[47] The cyst may be collapsed after discharge of its contents into the free peritoneal cavity. However, treatment of the cyst has relieved the ascites.[11] Rupture of the main pancreatic duct with juice exuding from a small hole on the surface of the gland has also been found. When no source for leak of pancreatic juice can be identified but the nature of the ascitic fluid is not in doubt, the main pancreatic duct should be drained into a Roux-en-y defunctionalized loop of jejunum. This permits the leak to seal.[11] This lesion is apparently not so rare as it has been thought, since 13 per cent of one reported series of pseudocysts presented with pancreatic ascites.[41]

SUMMARY

Pseudocysts are fascinating lesions of the pancreas which present as upper abdominal masses in about 80 per cent of cases, but also as obstructive jaundice, intrasplenic and intra-left-renal masses, mediastinal masses, flank abscess, pleural effusions, and ascites rich in amylase. They are diagnosed by urine amylase with greater sensitivity than by serum amylase. Cysts must be differentiated from pancreatic abscesses, indolent phlegmonous pancreatitis, cystadenomas, and carcinomas of the pancreas, as well as lymphomas and other rare tumors. They may be satisfactorily treated by large sump tube drains to the outside but about one third will require a further operation. Internal drainage by cystogastrostomy is the simplest and best current procedure, but not applicable to all cases. A good alternative is Roux-en-y cyst-jejunostomy. Caution is needed in the preoperative workup since all procedures are accompanied by an operative mortality approaching 10 per cent, mostly due to hepatic disease, portal hypertension, stress ulcerations, and hemorrhage. The follow-up shows 85 per cent good results from proper drainage but 40 per cent are diabetics and in many patients the ravages of alcoholism continue unabated.

RERFERENCES

1. Abrams, R. M., Beranbaum, E. R., Beranbaum, S. L., et al.: Angiographic studies of benign and malignant cystadenoma of the pancreas. Radiology, *89*:1028–1032, 1967.
2. Anderson, C. B., Connors, J. P., Mejia, D. C., et al.: Drainage methods in the treatment of pancreatic injuries. Surg. Gynec. Obstet., *138*:587–590, 1974.
3. Anderson, M. C.: Management of pancreatic pseudocysts. Amer. J. Surg., *123*:209–221, 1972.
4. Anderson, M. C.: Review of pancreatic disease. Surgery, *66*:434–449, 1969.
5. Anderson, W. J., Skinner, D. B., Zuidema, G. D., et al.: Chronic pancreatic pleural effusions. Surg. Gynec. Obstet., *137*:827–830, 1973.

6. Becker, W. F., Pratt, H. S., and Ganji, H.: Pseudocysts of the pancreas. Surg. Gynec. Obstet., *127*:744, 1968.
7. Becker, W. F., Welsh, R. A., and Pratt, H. S.: Cystadenoma and cystadenocarcinoma of the pancreas. Ann. Surg., *161*:845, 1965.
8. Bolooki, H., Jaffe, B., and Gliedman, M. L.: Pancreatic abscesses and lesser omental sac collections. Surg. Gynec. Obstet., *126*:1301, 1968.
9. Bradley, E. L., III, and Clements, J. J., Jr.: Implications of diagnostic ultrasound in the surgical management of pancreatic pseudocysts. Amer. J. Surg., *127*:163–173, 1974.
10. Buck, B. A., and Fletcher, W. S.: Carcinoma associated with pancreatic cyst. Surg. Gynec. Obstet., *134*:44–46, 1972.
11. Cameron, J. L., Brawley, R. K., Bender, H. W., et al.: The treatment of pancreatic ascites. Ann. Surg., *170*:668, 1969.
12. Caravait, C. M., Ashworth, J. S., and Frederick, P.: Pancreatic pseudocysts. J.A.M.A,, *197*:572, 1966.
13. Cerilli, J., and Faris, T. D.: Pancreatic pseudocysts: Delayed versus immediate treatment. Surgery, *61*:541, 1967.
14. Chetlin, S. H., and Elliott, D. W.: Preoperative antibiotics in biliary surgery. Arch. Surg., *107*:319–323, 1973.
15. Elliott, D. W.: Effect of lost pancreatic juice on gastric acid and peptic ulcer. Amer. J. Surg., *127*:658–662, 1974.
16. Elliott, D. W.: Non-operative management of acute pancreatitis. *In* Ellison, Friesen, Mulholland, eds.: Current Surgical Management. Vol. III. Philadelphia, W. B. Saunders Co., 1965, pp. 151–159.
17. Folk, F. A., and Freeark, R. J.: Reoperations for pancreatic pseudocyst. Arch. Surg., *100*:430, 1970.
18. Fox, N. M., Jr., Ferris, D. O., Moertel, C. G., et al.: Pseudocyst co-existent with pancreatic carcinoma. Ann. Surg., *158*:971, 1963.
19. Frey, C. F.: The operative treatment of pancreatitis. Arch. Surg., *98*:406–416, 1969.
20. Gilman, P. K., Gibbons, J. C., Kaplan, M. S., et al.: Unusual diagnostic aspects and current management of pancreatic pseudocysts. Amer. Surgeon, *40*:326–334, 1974.
21. Gonzalez, L. L., Jaffe, M. S., Wiot, J. F., et al.: Pancreatic pseudocyst: A cause of obstructive jaundice. Ann. Surg., *161*:569, 1965.
22. Greenstein, A., DeMaio, E. F., and Nabseth, D. C.: Acute hemorrhage associated with pancreatic pseudocysts. Surgery, *69*:56, 1971.
23. Hutson, D. G., Zeppa, R., and Warren, W. D.: Prevention of postoperative hemorrhage after pancreatic cystogastrostomy. Ann. Surg., *177*:689–693, 1973.
24. Jaffe, B. M., Ferguson, T. B., Holtz, S., et al.: Mediastinal pancreatic pseudocysts, Amer. J. Surg., *124*:600–606, 1972.
25. Jensen, F., and Pedersen, J. F.: The value of ultrasonic scanning in the diagnosis of intra-abdominal abscesses and hematomas. Surg. Gynec. Obstet., *139*:326–328, 1974.
26. Johnston, F. R., and Myers, R. T.: Etiologic factors and consequences of splenic vein obstruction. Ann. Surg., *177*:736–739, 1973.
27. Jones, R. C., and Shires, G. T.: Pancreatic trauma. Arch. Surg., *102*:424–430, 1971.
28. Karlan, M., McPherson, R. C., and Watman, R. N.: Experimental production of pseudocysts of the pancreas of the dog. Surg. Gynec. Obstet., *107*:221–227, 1958.
29. Katz, P., Dorman, M. J., and Aufses, A. H., Jr.: Colonic necrosis complicating postoperative pancreatitis. Ann. Surg., *179*:403–405, 1974.
30. Marks, E., Bank, S., Louw, J. H., et al.: Peptic ulceration and gastrointestinal bleeding in pancreatitis. Gut, *8*:253, 1967.
31. Miller, T. A., Lindenauer, S. M., Frey, C. F., et al.: Pancreatic abscess. Arch. Surg., *108*:545–551, 1974.
32. Miridjanian, A., Abruoso, V. N., Derby, B. M., et al.: Massive bilateral hemorrhagic pleural effusions in chronic relapsing pancreatitis. Arch. Surg., *98*:62, 1969.
33. Nardi, G. L., Lyon, D. C., Sheiner, H. J., et al.: Solitary occult retention cysts of the pancreas. New Eng. J. Med., *280*:11–15, 1969.
34. Othersen, H. B., Moore, F. T., and Boles, E. T.: Traumatic pancreatitis and pseudocyst in childhood. J. Trauma, *8*:535–546, 1968.
35. Parshall, W. A., and Remine, W. H.: Internal drainage of pseudocysts of the pancreas. Arch. Surg., *91*:480, 1965.
36. Polk, H. J., and Lopez-Mayor, J. F.: Postoperative wound infections: A prospective study of determinate factors and prevention. Surgery, *66*:97–103, 1969.
37. Polk, H. C., Zeppa, R., and Warren, W. D.: Surgical significance of differentiation between acute and chronic pancreatic collections. Ann. Surg., *169*:444, 1969.
38. Puestow, C. B., and Gillesby, W. J.: Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. Arch. Surg., *76*:989, 1958.
39. Rau, R. M., II, Thompson, R. J., Simmons, C. R., et al.: Selective visceral angiography in the diagnosis and treatment of gastrointestinal hemorrhage. Amer. J. Surg., *128*:160–167, 1974.

40. Rogers, J. B., Pearce, A. E., and Howard, J. M.: "Blue-dome" pseudocyst of the pancreas. Amer. J. Surg., *120*:813, 1970.
41. Rosenberg, I. K., Kahn, J. A., and Walt, A. J.: Surgical experience with pancreatic pseudocysts. Amer. J. Surg., *117*:11, 1969.
42. Salvo, A. F., and Nematolahi, H.: Distant dissection of a pancreatic pseudocyst into the right groin. Amer. J. Surg., *126*:430–432, 1973.
43. Scharplatz, D., and White, T. T.: A review of 64 patients with pancreatic cysts. Ann. Surg., *176*:638–640, 1972.
44. Schecter, L. M., Gordon, H. E., and Passaro, E., Jr.: Massive hemorrhage from the celiac axis in pancreatitis. Amer. J. Surg., *128*:301–305, 1974.
45. Schumer, W., McDonald, G. O., Nichols, R. L., et al.: Transgastric cystogastrostomy. Surg. Gynec. Obstet., *137*:48–50, 1973.
46. Shafer, R. B., and Silvis, S. E.: Pancreatic pseudo-pseudocysts. Amer. J. Surg., *127*:320–325, 1974.
47. Smith, R. B., Warren, W. D., Rivard, A. A., et al.: Pancreatic ascites. Ann. Surg., *177*:538–546, 1973.
48. Stept, L. A., Johnson, S. H., III., Marshall, M., Jr., et al.: Intrarenal pancreatic disease. J. Urol., *106*:17–18, 1971.
49. Stuber, J. L., Templeton, A. W., and Bishop, K.: Sonographic diagnosis of pancreatic lesions. Amer. J. Radiol., *116*:406–412, 1972.
50. Sybers, H. D., Shelp, W. D., and Morrissey, J. F.: Pseudocyst of the pancreas with fistulous extension into the neck. New Eng. J. Med., *278*:1058, 1968.
51. Thomford, N. R., and Jesseph, J. E.: Pseudocyst of the pancreas: A review of fifty cases. Amer. J. Surg., *118*:86, 1969.
52. Vajcner, A., and Nicoloff, D.: Pseudocysts of the pancreas: Value of urine and serum amylase levels. Surgery, *66*:842–845, 1969.
53. Vickers, F. N., and McPherson, R. C.: Cyst-gastrostomy stomal closure. Arch. Surg., *90*:1, 1965.
54. Warren, K. W., Athanassiades, S., Frederick, P., et al.: Surgical treatment of pancreatic cysts: Review of 183 cases. Ann. Surg., *163*:886, 1966.
55. Warren, K. W., and Badosa, F.: Individualization in treatment of pancreatic cysts. Amer. Surgeon, *39*:555–561, 1973.
56. Warren, W. D., Marsh, W. H., and Muller, W. H.: Experimental production of pseudocysts of the pancreas with preliminary observations on internal drainage. Surg. Gynec. Obstet., *105*:385, 1957.
57. Warshaw, A. L.: Inflammatory masses following acute pancreatitis. Surg. Clin. N. Amer., *54*:621–637, 1974.
58. Warshaw, A. L.: Pancreatic abscesses. New Eng. J. Med., *287*:1234–1236, 1972.
59. Warshaw, A. L., Chesney, T., Evans, G. W., et al.: Intrasplenic dissection by pancreatic pseudocysts. New Eng. J. Med., *287*:72–75, 1972.
60. White, T. T., and Bourde, J.: A new observation on human intraductal pancreatic pressure. Surg. Gynec. Obstet., *130*:275, 1970.
61. Wolstenholme, J. T.: Major gastrointestinal hemorrhage associated with pancreatic pseudocyst. Amer. J. Surg., *127*:377–381, 1974.

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Pancreatic Cancer

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Diagnostic and therapeutic advances of the last 30 years have left unchanged the course and prognosis of carcinoma of the exocrine pancreas. The most important reasons for this are the anatomic location and biologic nature of the tumor. An additional factor of importance is the consistently reported 4 to 9 month delay in diagnosis,[6, 29] also unchanged in 30 years. Recent controversy has developed concerning the mainstay of our current surgical treatment, the Whipple pancreaticoduodenectomy and its modifications, and its role as the most efficacious surgical approach to this disease.

It is the purpose of this paper to review and summarize the clinical characteristics of carcinoma of the exocrine pancreas and to review and reassess the standard operative approach. Cancer of the head, body, and tail of the pancreas will be considered together because they have many features in common.

CLINICAL FEATURES

The failure of technical advances to improve the prognosis for patients with cancer of the pancreas over the last 30 years points to the need for a thorough review of the clinical signs and symptoms of this discouraging disease. This review is even more indicated by the frequently reported 4 to 9 month delay from onset of first symptoms to diagnosis. It should be noted that many of the early features of carcinoma of the pancreas have been identified by retrospective case analysis. Hopefully, as clinical and diagnostic acumen improve, some of the more common and less favorable signs and symptoms will assume a lower order of prominence in future series.

It should be stressed that the initial symptoms of cancer of the pancreas are often vague and that, above all, physicians must employ a high index of suspicion if earlier diagnosis is to be effected.

Weight Loss. Weight loss probably has been the most common

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symptom seen.[4, 6, 31, 58] Associated usually, but not necessarily, with anorexia, it may be rapid and severe. Berk,[6] in a collected series of 813 patients reported an average weight loss of 11.9 kg at the time of admission.

PAIN. Abdominal pain afflicts 50 to 90 per cent of patients at sometime in the course of their illness.[4-6, 20, 21, 29, 31, 58] It has been reported as the most common initial symptom in several retrospective series, but it is probable that other less specific symptoms actually precede the onset of pain in most patients.

The insidious onset of intermittent, dull, vague, or aching epigastric pain, perhaps aggravated by meals or associated with post-cibal fullness or bloating, is a characteristic early description. The epigastric location is based on a T7 to T10 nerve distribution. The initial pain has been reported to occur in the hypogastrium in up to 10 per cent of patients. Colicky pain is not unusual and is more common when the pain is in the right upper quadrant, mimicking biliary colic. Right upper quadrant pain from pancreatic cancer bespeaks involvement of the head of the gland. Left upper quadrant pain is not unusual either, may be colicky, and suggests cancer of the body and/or tail of the pancreas. Initially, the pain is unlikely to penetrate through to the back, but may do so if there is associated pancreatitis. Back pain alone has been reported, but is uncommon as the only presenting symptom.

As the disease progresses, especially when the posterior parietes or surrounding viscera are involved, the pain becomes progressively more severe and constant and is often associated with penetration to the back. It may assume a boring quality. If there is ductal obstruction, aggravation by meals may be pronounced. The pain is often described as being worse at night, aggravated by recumbency, and ameliorated by lying with legs drawn up, or walking bent over.

MENTAL SYMPTOMS. Mental or psychiatric symptoms associated with carcinoma of the pancreas are little understood and often neglected, particularly since they are not amenable to retrospective analyses. Fras et al.[28] interviewed, prior to any definitive therapy, 46 patients with carcinoma of the pancreas and 64 patients with colon cancer; 48 per cent of the former patients told of mental symptoms as the first to be experienced. These were described as depression, loss of ambition, interest, or initiative, and an unusual feeling of anxiety or premonition of serious illness. The onset of these symptoms always preceded and never followed the onset of pain. Seventy-six per cent of the patients with pancreatic cancer reported psychiatric symptoms in the course of the illness prior to operation. The overall incidence of psychiatric symptoms in patients with cancer of the colon was only 17 per cent. It is possible that reports which refer to fatigue as a common symptom are in fact documenting the symptoms described above.

JAUNDICE. Along with weight loss and pain, jaundice is certainly one of the "big three" symptoms of cancer of the pancreas. It is more common with cancer of the head of the gland, being present in 80 to 90 per cent of patients sometime in the course of the disease.[5, 6, 61] When present, it is usually relentless and progressive, but may be intermittent.

The popular misconception that painless jaundice is the sine qua non of cancer of the head of the gland persists despite repeated reports that it occurs in only 15 to 25 per cent of patients.[5, 6, 20] Jaundice with pain is more common by far. Another popular misconception refers to the fact that jaundice per se indicates unresectability or even inoperability. It is incumbent upon the medical team to demonstrate distant metastases or local extension before deciding that a jaundiced patient's tumor is not resectable.

Bowel Disturbance. Diarrhea and/or constipation is seen in 10 to 50 per cent of cases[4, 5, 20, 21, 29, 40, 58] and has been reported as initial symptoms in as high as 30 per cent of cases. The diarrhea may be steatorrheic in nature, but usually is not.

Thrombophlebitis and Phlebothrombosis. Migratory thrombophlebitis has commanded much more medical attention as a symptom of pancreatic cancer than it deserves.[5, 30, 31, 34] While this entity requires full diagnostic investigation, it is not pathognomonic of pancreatic cancer and does not by itself justify exploratory laparotomy. At necropsy, phlebothrombosis has been reported in up to 50 per cent of patients with cancer of the body and tail of the gland.[56] However, this is a terminal complication of many chronic diseases and may be seen in up to 50 per cent of middle-aged or elderly patients dying of cancer or heart failure.[5]

Dyspepsia, Nausea, Vomiting. Vague symptoms of dyspepsia, nausea, and epigastric or post-cibal fullness are not uncommon early symptoms, but they are sufficiently vague or subjective to be little value in themselves. It has been suggested that these symptoms may be related to the achlorhydria which has been reported in patients with pancreatic cancer.[16] Nausea and vomiting are seen in 10 to 30 per cent and, generally, are due to duodenal obstruction.[6]

Pruritus. Pruritus, a common accompaniment to obstructive jaundice, may be seen in 10 to 20 per cent of cases.[4, 37, 60] It bears no specific relationship to pancreatic cancer.

Chills and Fever. Chills and fever are seen occasionally[4, 20, 29] and may raise the level of clinical suspicion sufficiently to be helpful if there is not another obvious cause or if there are associated symptoms.

Hematemesis and Melena. Hematemesis and melena are usually late symptoms and may be due to tumor extension into the duodenum or stomach with ulceration, duodenal obstruction with benign gastric ulceration, or secondary to portal compression and resultant esophageal varices.

Hepatomegaly. Liver enlargement is recorded in 50 to 65 per cent of cases[4, 29, 31, 58] and is more common in carcinoma of the head of the gland. It is seen in 90 per cent of jaundiced patients[60] and is thought to be due to biliary obstruction and/or fatty infiltration rather than hepatic metastases. As with jaundice, hepatomegaly is not in itself a criterion of inoperability.

Palpable Gallbladder. The classic observation by Courvoisier that a palpable gallbladder in the presence of painless jaundice should always suggest malignant disease is certainly true, but if a palpable

gallbladder is not found, the presence of carcinoma is not excluded. A clinically enlarged gallbladder has been reported in 12 to 50 per cent of cases of carcinoma of the head of the gland[6, 13, 29, 31, 58] and is more likely to be present when there is jaundice. Even higher percentages (60 to 90 per cent) are reported at the time of laparotomy or necropsy.

MISCELLANEOUS. An epigastric abdominal mass is palpable in 10 to 20 per cent of cases[4] and may be movable. Abdominal tenderness may be present in up to one third of patients with lesions of the body and tail.[21] An often overlooked sign is that of an abdominal bruit. This usually is due to splenic artery compression or involvement. Abdominal enlargement due to ascites, a neck mass or subcutaneous nodules are signs sometimes seen in patients at the time of admission and, obviously presage a hopeless prognosis.

DIAGNOSTIC STUDIES

LABORATORY VALUES. The most common abnormal laboratory studies are those which reflect obstructive jaundice and are most often abnormal with carcinomas of the head of the gland. The serum alkaline phosphatase is usually elevated first, followed by the direct-reacting bilirubin. The indirect-reacting fraction rises soon after the direct, often precluding a definitive diagnosis of the type of jaundice. Quantitative urobilinogen of less than 5 mg in 24 hours is helpful in indicating obstructive jaundice. Serum glutamic oxalic transaminase is helpful in excluding hepatitis, values below 500 mg being the rule. Urinary amylase may be elevated with cancers of the head of the pancreas, but is rarely so with body and tail lesions. Serum amylase and lipase are not usually elevated. An abnormal prothrombin time is usually indicative of primary hepatocellular disease but may be seen if obstructive jaundice has been longstanding.

Elevated fecal fat and undigested meat fibers in the stool may help in the diagnosis of lesions of the head of the gland, but usually are not seen with body and tail lesions. Positive stool guaiac may be present in up to 50 per cent of cases even with tumors of the body and tail.[21] Fasting hyperglycemia, glycosuria, or abnormal glucose tolerance test are present in 20 to 50 per cent of reported cases.[5, 6, 38] It should be stressed that an abnormal glucose tolerance test is often present without glycosuria or fasting hyperglycemia. Elevated BSP retention and hypoalbuminemia are not uncommon, but, of course, are not diagnostic.

Secretin Studies

The secretin and secretin-pancreozymin tests have been shown to be of value in studying the function of the exocrine pancreas.[23, 46] In the former test, deficiency of volume of pancreatic juice below 2 ml per kg over 80 minutes is characteristic of lesions obstructing the pancreatic duct while a qualitative deficiency of bicarbonate below 90 mEq per liter is associated with inflammatory disease. This is a less reliable test for tumors of the body and tail. However, when coupled with the collec-

tion of cells for cytologic study, the secretin test and secretin-pancreozymin test, particularly the latter, may yield a cytologic diagnosis of malignancy in 80 per cent of cases,[23] including those with tumors of the body and tail.

Special Tests

In cases in which the nature of the jaundice is unclear, the prednisolone test has been used to distinguish primary intrahepatic disease from obstructive jaundice. Thirty mg of prednisolone per day is given for 7 days and should cause a rapid drop in bilirubin during the first few days if the jaundice is not obstructive in nature.

Radiologic Procedures

An upper gastrointestinal barium meal may be helpful in one third of patients with cancer of the head of the gland. Widening of the duodenal c-loop, the "inverted three" sign, and evidence of external compression, erosion or irregularity of the duodenum are commonly looked for signs. Distortion and flattening of the gastric antrum, rigidity of the gastric wall, anterior displacement of the stomach, or displacement of the colon may be seen with tumors of the body and tail, but radiologic abnormalities are even less frequent than with lesions of the head of the organ.

Hypotonic duodenography is probably more helpful in the diagnosis of tumors of the head of the pancreas than a standard barium meal.

If the serum bilirubin is below 3, oral cholecystography or intravenous cholangiography may be useful methods with which to assess the biliary tract. In patients with obstructive jaundice, percutaneous transhepatic cholangiography may be helpful in defining the cause of the jaundice.

In general, it can safely be said that rarely is a definitive diagnosis made possible by standard radiologic techniques, but an abnormal x-ray in association with a suggestive history and physical examination is strong confirmatory evidence.

Fiberoptic duodenoscopy with cannulation of the papilla and pancreatic ductography is a new and exciting procedure which is not commonly employed at present, but which may prove to be of more use in the future.

Angiography of the celiac and mesenteric arteries has been more helpful in the diagnosis of endocrine tumors of the pancreas than in the diagnosis of exocrine cancers. However, selective pancreatic angiography has been successfully employed to differentiate cancer from pancreatitis, to locate the tumor, and to evaluate operability.[7] Angiography and splenoportography will be discussed in more detail in a subsequent section.

Retroperitoneal pneumatography has proved to be of little value in the diagnosis of pancreatic cancer.

Scanning

^{75}Se-selenomethionine is the best evaluated and most commonly used scanning agent. Electronic subtraction of the liver image and

sequential imaging have contributed to the diagnostic accuracy with which scanning may be used. For a more thorough discussion of this topic, the reader is referred to a recent review by Bachrach et al.[3]

Pancreatic scanning, as it is currently performed, contributes little to the diagnosis of pancreatic cancer at an early stage. In most instances in which the scan is clearly abnormal, the symptomatology, laboratory studies and/or radiologic findings are sufficiently abnormal to point to the need for exploratory laparotomy without further delay.

Laparotomy

Exploratory laparotomy remains the sine qua non in the diagnosis of pancreatic cancer. As Whipple has said, "To observe the patient for weeks until the diagnosis is obvious is to study the patient to death." If there is any confirmatory laboratory or radiologic evidence, the patient should have a laparotomy performed. Even if a cytologic diagnosis is in hand, a patient with a clinically obvious carcinoma of the pancreas in whom there is no evidence of distant metastasis should almost always have a laparotomy to determine the regional extent of the disease. It is axiomatic that this should be undertaken only by a surgeon familiar with the disease and prepared to proceed with definitive surgical treatment. A previous exploration, particularly if there has been a biopsy, makes an assessment of the extent of the tumor by the surgeon more difficult, increases the technical difficulty of resection, and reduces the chances for cure.

Biopsy

One of the more controversial areas relative to the diagnosis of cancer of the pancreas has to do with peroperative biopsy. Many believe that the morbidity and even mortality associated with peroperative biopsy are inordinately high and that the lack of a definitive diagnosis is all too common. They argue that in many cases a negative biopsy will not change the surgeon's decision to do a resection. Other surgeons believe that a biopsy-proven diagnosis should always be obtained prior to the performance of radical surgical procedures.

In cases in which there is an obvious pancreatic cancer or in which a histologic diagnosis can be obtained by biopsy of a regional lymph node or tumor mass, there should be no need for a pancreatic biopsy. However, it is in such cases as those in which the clinical diagnosis is difficult (i.e., a small tumor surrounded by a zone of pancreatitis) that the decision to biopsy has proven to be so controversial. Both needle puncture biopsy and wedge biopsy have been reported to be attended by an unacceptable morbidity and mortality from complications such as pancreatitis, pancreatic fistula, abscess and pseudocyst formation, hemorrhage, and false positive and negative diagnoses. In addition, the possibility of tumor dissemination has been raised as an objection. However, Dencker[20] and Forsgren[27] report a reliability rate of 80 to 90 per cent and a complication rate of only 4 per cent with one mortality when these two techniques were used to evaluate a total of 131 patients.

Aspiration biopsy with a small gauge needle is a newer technique

which appears to be less controversial. Forsgren,[26] Christoffersen and Poll,[15] and Halveg[33] have reported a total of 77 patients on whom aspiration biopsies of the pancreas were done. There was one false negative diagnosis, no false positive diagnoses and no complications or mortalities. As to whether or not aspiration biopsies might disseminate tumor, there is evidence that they do not from large series of cancer of the breast (Robbins et al.),[5] kidney (von Schrieb),[57] and salivary gland (Engzell).[24]

PATHOLOGY

Cancer of the pancreas occurs in the head of the gland in 65 per cent of cases.[32, 41] In only 10 per cent of the 2436 cases collected by the California Public Health Department between 1942 and 1956 was the tumor still localized within the gland at operation.[12]

GROSS DESCRIPTION. Pancreatic cancer is a poorly demarcated gray-brown, schirrhous, nodular growth within the glandular substance. When cut with a scalpel it is hard and gritty. The cut surface may show scattered areas of red or brown necrosis or hemorrhage. Spaces containing turbid, gray or brown fluid may be present. Spread beyond the capsule tends to be in the form of hard, bulging masses of irregular conformation. Occasionally, the pancreas is diffusely involved and there is no distortion. Lesions which result in ductal obstruction may cause the duct of Wirsung to be enlarged and palpable and the body and tail to be indurated and firm with rounded or blunted edges. In such cases there may be signs of pancreatitis such as fat necrosis.

PATHS OF SPREAD. Carcinoma of the head of the pancreas is characterized by invasion into and along the duct of Wirsung and common bile duct and into the duodenum. The stomach and portal vein may be directly invaded. In cancer of the body and tail, direct invasion of the posterior parietes and splenic vein are common and seeding into the peritoneal cavity is more frequently seen than with lesions of the head. The liver, regional lymph nodes, and lungs are the most common sites of metastases. Distant lymph nodes, adrenal glands and peritoneum are less common sites.

Three anatomic characteristics favor the early dissemination of pancreatic cancer: (1) the rich lymphatic drainage of the pancreas and the absence of acinar lymphatic capillaries; (2) the rich venous drainage by short, large vessels which drain into the splenic and portal veins; (3) the intimate relationship of the pancreas to other intra-abdominal organs such as the duodenum, common bile duct, stomach, colon and spleen.

HISTOLOGY. The most common histologic tumor type is adenocarcinoma of ductal cell origin, occurring in 80 to 90 per cent of cases. The remainder arise from the acini. Variations of ductal carcinomas may include squamous carcinoma (adenoacanthoma), mucinous carcinoma and ciliated adenocarcinoma. Involvement of the perineural lymphatics and microvasculature of the gland are common and presages a poorer prognosis.

OPERATIVE MANAGEMENT

SURGICAL PROCEDURES

At the present time operative treatment is the only effective therapy for carcinoma of the pancreas. Despite the relatively poor prognosis, surgical cures are possible. No patient should be denied the chance for a cure just because his physician believes that cancer of the pancreas is a uniformly lethal disease.

A thorough exploration of the abdominal cavity and evaluation of the periampullary area, lesser sac, parietes posterior to the pancreas, and regional lymph node–bearing areas are necessary prior to deciding whether or not a tumor is resectable. The most frequently involved lymph nodes are those at the root of the small bowel mesentery, those along the hepatic, middle colic, splenic and gastroepiploic arteries, those posterior to the common and hepatic ducts, and those at the celiac axis. Peritoneal seeding, liver involvement, portal or mesenteric vascular involvement, extension into the posterior parietes, complete involvement of the uncinate process and regional lymphatic involvement are generally thought to preclude resection for cure. In most series, resectability varies from 10 to 20 per cent.[17, 35, 43]

For descriptions of the "Whipple pancreaticoduodenectomy" and its modifications, hereinafter called partial pancreatectomy, the reader is referred to Waugh and Gilberson,[63] Warren and Jefferson,[62] and Child and Frey.[14] In general, these operations involve a regional, en bloc resection of the distal half of the stomach and common bile duct, the entire duodenum, and the head and neck and a variable portion of the body of the pancreas. The extent of the gastrectomy depends upon whether or not a vagotomy is to be done (i.e., antrectomy when vagotomy is done, two thirds gastrectomy when no vagotomy is done). Reconstruction is usually accomplished from proximal to distal by a choledochojejunostomy, pancreaticojejunostomy, and, finally, a gastrojejunostomy. There is no unanimity of opinion as to what is the best method of constructing the pancreaticojejunal anastomosis, that is, whether direct duct to jejunum suturing is necessary, or whether invagination of the entire transected surface of the pancreas into the jejunum is just as good or preferable.

For cancers of the body and tail, distal pancreatectomy and splenectomy are the most commonly employed procedures.

En bloc resection of the common bile duct, stomach, duodenum, pancreas, and spleen, hereinafter termed total pancreatectomy, is an increasingly popular operation for cancers of the pancreas. For a description of this operation refer to Ross.[51] The rationale for total pancreatectomy will be discussed.

Temporizing Procedures

If a pancreatic neoplasm is found at operation in a jaundiced patient by a surgeon unwilling or unable to perform a definitive resection, the occasion may be utilized with benefit if he performs cholecystostomy or

T-tube choledochostomy. This is also done by some surgeons as part of a two-stage approach in patients who are severely jaundiced. There is some indication that preliminary biliary decompression in the jaundiced patient lowers the postoperative morbidity and mortality from hepatic and renal insufficiency.[43, 62]

Palliation

Several palliative procedures may be considered for unresectable cancers of the pancreas. Biliary diversion with a Roux-en-Y loop of jejunum is indicated for advanced lesions of the head of the gland. A choledochojejunostomy may be preferable to a cholecystojejunostomy because of the tendency of lesions of the head to extend and obstruct the common bile duct.

Duodenal obstruction by tumors of the head of the gland may be palliated by a gastrojejunostomy. Indeed, for these lesions, gastrojejunostomy should be done at the time of biliary diversion, since duodenal obstruction is imminent in many cases in which it does not already exist.

The mean survival time for patients undergoing bypass procedures is 5 to 9 months.[2, 40, 62] Though they obviously do not prolong survival, these procedures are certainly of use in improving the quality of remaining life.

Postoperative Morbidity, Mortality, and Survival

The early postoperative morbidity associated with the "Whipple" pancreaticoduodenectomy is not small. Monge[43] reported significant postoperative complications in 65 per cent of 236 patients undergoing this procedure. Pancreatic and biliary fistulas, gastrointestinal hemorrhage, wound infections, hypotension and peritonitis lead the list of complications. Uremia was present in 38 per cent of patients and primary renal failure accounted for 11 per cent of the deaths. Unfortunately, this experience with partial pancreatectomy is not unique. In most series pancreatic fistula, with or without intraperitoneal hemorrhage, peritonitis, or sepsis, is the leading cause of morbidity and death.[2, 4, 43, 59] In the series of 253 patients reported by the Lahey Clinic,[61] the late postoperative complications consisted of pancreatic exocrine insufficiency (22.0 per cent), diabetes mellitus (15.0 per cent), and jejunal ulcer (7.5 per cent). It is probable that these rates would have been higher, had patients survived longer. Although series of 25[54] and 41[36] cases of pancreaticoduodenectomy without an operative mortality have been reported, the general experience with this operation has not been so fortunate, with postoperative mortality ranging from 13.5 to 51 per cent.[4, 19, 31, 40, 43, 49] In general, the operative mortality varies considerably with the surgeon and with the institution, but 25 to 30 per cent is probably not far from the average rate over the past 10 years.

Five-year survival rates after pancreaticoduodenectomy for cancer of the head of the pancreas vary from 0 to 14 per cent.[31, 40, 43, 61] There is only one reported case of a 5 year survival after resection for carcinoma of the body and tail of the pancreas.[21] The average survival after pallia-

tive bypass procedures ranges from 4 to 9 months. Morris and Nardi[44] compared a group whose tumors were resected to another group whose tumors were resectable, but in whom palliative bypass procedures were done instead. Fifty per cent of the latter group were dead at 6 months, whereas 50 per cent of the former group were alive at 21 months.

A CASE FOR TOTAL PANCREATECTOMY

The dismal survival rates which have been achieved by partial pancreatectomy have stimulated surgeons to consider total pancreatectomy as a way of achieving more cures. There are several factors which would lead one to believe that this might be possible:

1. Cancer of the pancreas may be a multicentric disease. Though the exact incidence of multicentricity is not known, a high incidence of ductal hyperplasia and even carcinoma in situ have been reported in association with invasive cancers of the pancreas.[17, 55] In addition, a high incidence of ductal hyperplasia has been reported on autopsies of diabetics,[55] a group known to be at higher risk for cancer of the pancreas.[5, 6, 38]

2. Invasive cancer at the line of resection has been documented in a total of 15 of 50 cases reported by Monge et al.,[42] Collins et al.,[17] and Hicks et al.[35] Though poorly documented in most series, the recurrence of tumor in the pancreatic remnant is frequent enough to suggest that pancreatic tissue containing tumor is left behind in some proportion of cases.

3. Free-floating malignant cells have been found within the ductal system[14] and could result in seeding of the operative site or remaining duct system. The high rate of positive cytologic diagnosis with secretin stimulation[23] tends to confirm this possibility.

4. Cancer of the pancreas is diffuse in approximately 6 per cent of cases.[31]

5. Complications relative to the pancreaticojejunal anastomosis, the major cause of morbidity and death after partial pancreatectomy, is eliminated by total pancreatectomy.

There are several reasons why total pancreatectomy has not gained the popularity that it might otherwise enjoy:

1. The diabetic state resulting from total pancreatectomy has been considered difficult to manage. In addition, the possibility exists that patients will develop the long-term sequelae of diabetes mellitus, i.e., retinopathy, nephrosclerosis, and vascular disease.

2. The total loss of pancreatic exocrine secretion has been viewed as a major problem in postoperative management.

3. The mortality rates reported in early total pancreatectomy series were much higher than those presently attainable for partial pancreatectomy.

These problems deserve a more thorough discussion than they have yet been given.

Diabetic State

Early reports[34, 45] of patients who had had total pancreatectomy indicated that these patients behaved as brittle diabetics. Their insulin

requirements fluctuated widely and precipitously and hypoglycemic episodes were common. However, many of these cases had recurrent tumor, unsuspected infections, or poor and erratic intestinal absorption because of a failure to take pancreatic exocrine supplements. In addition, the diabetic control which was attempted was probably too strict. Most recent reports indicate that the diabetes produced by total pancreatectomy is not of the brittle type and is not difficult to manage. The early postoperative insulin doses are not high, even in patients with pre-existing diabetes, and often decrease with time. It is generally agreed that the aim of insulin therapy should be to prevent ketosis, but not to maintain the patient in a euglycemic state, or even necessarily to prevent glycosuria.

Given the facts that 25 to 50 per cent of patients have diabetic glucose tolerance curves prior to operation and that insulin-requiring diabetes develops as a late sequela of partial pancreatectomy in approximately 15 per cent of patients, an inordinate concern over producing a diabetic state by total pancreatectomy does not seem justified. One case of diabetic retinopathy[11] and one case of total diabetic nephrosclerosis[22] have been reported after total pancreatectomy. Unfortunately, there have not been enough long-term survivors to document the frequency of these late complications. Given the dismal survival rates after partial pancreatectomy and the age of peak incidence of cancer of the pancreas, it is unlikely that this will ever be a serious objection to total pancreatectomy.

Pancreatic Exocrine Function

The loss of pancreatic exocrine secretions after total pancreatectomy results in steatorrhea and creatorrhea. Recent reports indicate that a positive nitrogen balance and weight maintenance can be obtained with the use of commercial pancreatic supplements such as Pancreatin, Cotazyme (pancrelipase) and Viokase (pancreatic extract) when coupled with a reduced fat intake.[35, 49] The somewhat unpredictable response to pancreatic extracts seems to be due to variable lipase activity. The effectiveness with which these agents may be employed depends upon an adequate reduction in gastric acid production and points out the need for adequate gastrectomy and/or vagotomy. The late occurrence of exocrine insufficiency has been reported to be the most common sequela of partial pancreatectomy.[62] It often occurs as a result of tumor recurrence or consequent to anastomotic ductal stenosis. Since pancreatic exocrine insufficiency is almost always manageable and since it occurs frequently following partial pancreatectomy, the complete exocrine insufficiency of total pancreatectomy appears to be a weak argument against this procedure.

Mortality and Morbidity

The operative mortality after total pancreatectomy was high in early series. The same may be said of the "Whipple operation" and its modifications. Indeed, in some series the operative mortality is still in the 50 per cent range.[31, 40] More recently Hicks[35] has reported an operative mortality of 9 per cent and Remine[49] one of 22 per cent after total pancreatectomy.

With the pancreaticojejunal anastomosis accounting for at least 20 per cent of the morbidity and mortality after partial pancreatectomy, one would expect a lower morbidity after the total operation as more experience is gained.

Whether or not long-term survival will be improved following total pancreatectomy is uncertain. Hicks[35] reported an average survival of 15.4 months in 10 patients surviving total pancreatectomy, 2 patients being alive at 21 months and one alive at 4½ years. The average survival of 9 living after partial pancreatectomy was 8½ months. Remine[49] reported 18 patients surviving total pancreatectomy. Four were alive and well at the time of the report, 7 others lived beyond 2 years, 4 beyond 4 years and 2 beyond 5 years.

In summary, the replacement of partial pancreatectomy by total pancreatectomy in the surgical treatment of resectable cancers of the pancreas seems indicated. Comparable operative mortality, lower postoperative morbidity and higher survival rates may be anticipated.

NON-OPERATIVE MANAGEMENT

Management of the patient with unresectable cancers of the pancreas should be aimed at the relief of pain and improvement of the quality of remaining life. Narcotics for pain relief are obviously warranted but may not be effective. Bridenbaugh[9] reported acceptable results following injection of 50 per cent alcohol into the celiac plexus. Chemical splanchnicotomy at the time of exploration or bypass procedure has also been reported to be effective.[18] Though neither radiation therapy nor 5-fluorouracil treatment alone has been very effective in the relief of pain, together they have been reported to be beneficial by Falkson.[25]

5-Fluorouracil is probably the most thoroughly evaluated chemotherapeutic agent which has been used to treat cancer of the pancreas. Keementz and Becker[40] report occasional worthwhile responses. Combination chemotherapy appears to hold some promise of more objective responses but as yet has not been well evaluated.

HOPE FOR THE FUTURE

Some hope for better prognosis and cure rates may be forthcoming if earlier diagnosis is achieved and the operative approach is modified. It must be obvious, however, that the only real hope of major changes in survival is a better understanding of the oncogenesis of these tumors and, subsequently, the development of therapeutic modalities aimed at this process itself. At the present time, adjuvant immunotherapy and adjuvant combination chemotherapy hold some promise. It is imperative that these and, indeed, all promising treatment modalities be employed in the context of clinical trials, so that the dismal prognosis detailed herein is not repeated in a paper 30 years hence.

REFERENCES

1. American Cancer Society: 1971 Facts and Figures. American Cancer Society, New York, 1970.
2. Aston, S. J., et al. Pancreaticoduodenal resection. Twenty years experience. Arch. Surg., *106*:813, June 1973.
3. Bachrach, W. H., et al.: Pancreatic scanning: A review. Gastroenterology, *63*:890, 1972.
4. Baker, R. R., et al.: Carcinoma of the head of the pancreas and periampullary region. Johns Hopkins Med. J., *132*:212, April 1973.
5. Bell, E. T.: Carcinoma of the pancreas: I. A clinical and pathologic study of 609 necropsied cases. II. The relation of carcinoma of the pancreas to diabetes mellitus. Amer. J. Path., *33*:499, 1957.
6. Berk, J. E.: The diagnosis of carcinoma of the pancreas. Arch. Intern. Med., *68*:525, 1941.
7. Bookstein, J. J., et al.: Angiographic evaluation of pancreatic carcinoma. Radiology, *93*:757, 1969.
8. Braganza, J. M., and Howat, H. T.: Cancer of the pancreas. Clin. Gastroenterol., *1*:219, 1972.
9. Bridenbaugh, L. D., et al.: Management of upper abdominal cancer pain: Treatment with celiac plexus block with alcohol. J.A.M.A., *190*:877, 1964.
10. Burch, G. E., and Ansari, A.: Chronic alcoholism and carcinoma of the pancreas. Arch. Intern. Med., *122*:273, 1968.
11. Burton, T. Y., et al.: Diabetic retinopathy following total pancreatectomy. Mayo Clinic Proc., *32*:735, 1957.
12. Cancer Registration and Survival. California Department of Public Health, 1963, p. 35.
13. Cattell, R. B., et al.: Periampullary carcinomas: Diagnosis and surgical management. SURG. CLIN. N. AMER., *39*:781, 1959.
14. Child, C. G., and Frey, C. F.: Pancreaticoduodenectomy. SURG. CLIN. N. AMER., *46*:1201, 1966.
15. Christoffersen, P., and Poll, P.: Peroperative pancreas aspiration biopsies. ACTA Pathol. Microbiol. Scand. (Suppl)., *212*:28, 1970.
16. Clifton, E. E.: Carcinoma of the pancreas. Amer. J. Med., *21*:760, 1956.
17. Collins, J. J., et al.: Rationale for total pancreatectomy for carcinoma of the pancreatic head. New Eng. J. Med., *274*:599, 1966.
18. Copping, J., et al.: Palliative chemical splanchnicectomy. Arch. Surg., *98*:418, 1969.
19. Craighead, C. C., and Lien, R. C.: Pancreatico-duodenal resection. Comments on indications, operative diagnosis, staged procedures, morbid and lethal factors and survival. Ann. Surg., *147*:931, 1958.
20. Dencker, H.: Symptomatology of Resectable Periampullary Carcinoma. ACTA Chir. Scand., *138*:613, 1972.
21. Die Goyanes, A., et al.: Cancer of the body and tail of the pancreas. Rev. Surg., *28*:153, 1971.
22. Doyle, A. P., et al.: Fatal diabetic glomerulosclerosis after total pancreatectomy. New Eng. J. Med., *270*:623, 1964.
23. Dreiling, D. A.: The early diagnosis of pancreatic cancer. Scand. J. Gastroent., *5*(Suppl 6):115, 1970.
24. Engzell, U., et al.: Investigation on tumour spread in connection with aspiration biopsy. Acta Radiol. (Ther.), *10*:385, 1971.
25. Falkson, G., et al.: Combined telecobalt and 5-fluorouracil therapy in carcinoma of the pancreas: A Report of 97 Cases. South Afr. Med. J., *44*:444, 1970.
26. Forsgren, L., et al.: Aspiration cytology in carcinoma of the pancreas. Surgery, *73*:38, January 1973.
27. Forsgren, L., et al.: Pancreatic biopsy. Acta. Chir. Scand., *134*:457, 1968.
28. Fras, I., et al.: Comparison of psychiatric symptoms in Carcinoma of the pancreas with those in some other intra-abdominal neoplasms. Amer. J. Psychiat., *123*:1553, 1967.
29. Gambill, E. E.: Pancreatic and ampullary cancer: Diagnosis and prognosis in relationship to symptoms, physical findings and elapse of time as observed in 255 patients. South. Med. J., *63*:1119, 1970.
30. Gore, I.: Thrombosis and pancreatic carcinoma. Amer. J. Path., *29*:1093, 1953.
31. Gray, L. W., et al.: Carcinoma of the pancreas. Proc. Natl. Cancer Conf., *7*:503, 1973.
32. Gullick, H. D.: Carcinoma of the pancreas. A review and critical study of 100 cases. Medicine, *38*:47, 1959.
33. Halveg, A. B., et al.: Peroperative fine-needle aspiration biopsy. Acta Chir. Scand., *139*:452, 1973.
34. Harter, W. M., and Kuhl, W. J.: The effect of pancreatectomy on a patient with pre-existing diabetes mellitus. A case report and review of the literature. Diabetes, *11*:118, 1962.

35. Hicks, R. E., et al.: Total pancreatectomy for ductal carcinoma. Surg. Gynec. Obstet., *133*:16, July 1971.
36. Howard, J. M.: Pancreaticoduodenectomy: 41 consecutive Whipple resections without an operative mortality. Ann. Surg., *168*:629, 1968.
37. Howard, J. M., and Jordon, G. L., Jr.: Surgical Diseases of the Pancreas. Philadelphia, J. B. Lippincott Co., 1960, p. 463.
38. Karmody, A. J., and Kyle, J.: The association between carcinoma of the pancreas and diabetes mellitus. Brit. J. Surg., *56*:362, 1969.
39. Krain, L. S.: Cancer incidence: The crossing of the curves for stomach and pancreatic cancer. Digestion, 1972, p. 356.
40. Krementz, E. T., and Becker, M. L.: Malignant disease of the pancreas. Adv. Surg., *6*:205, 1972.
41. Miller, J. R., et al.: Carcinoma of the pancreas. Effect of histologic type and grade of malignancy on its behavior. Cancer, *4*:233, 1951.
42. Monge, J. J., et al.: Clinicopathologic observations on radical pancreaticoduodenal resection for periampullary carcinoma. Surg. Gynec. Obstet., *118*:275, 1964.
43. Monge, J. J., et al.: Radical pancreaticoduodenectomy: A 22 year experience with complications, mortality rate and survival rate. Ann. Surg., *160*:711, 1964.
44. Morris, G. E., and Nardi, G. L.: Pancreaticoduodenal cancer. Experience from 1951 to 1960 with a look ahead and behind. Arch. Surg., *92*:834, 1966.
45. McCullach, E. P., et al.: Diabetes following total pancreatectomy: Clinical observations of ten cases. Diabetes, *7*:298, 1958.
46. Olsen, J. H.: Duodenal exfoliative cytology. Diagnosis of cancer of duodenum, pancreas and biliary tract by exfoliative cytology. Scand. J. Gastroenterol., *6*(Suppl. 9):105, 1971.
47. Pancreas. End Results in Cancer: Report No. 4. U.S. Dept. of Health, Education and Welfare. Public Health Service. National Institutes of Health, 1972.
48. Porter, M. R.: Carcinoma of the pancreaticoduodenal area: Operability and choice of procedure. Ann. Surg., *148*:711, 1958.
49. Remine, W. H., et al.: Total Pancreatectomy. Ann. Surg., *172*:595, 1970.
50. Robbins, G. F., et al.: Is aspiration biopsy of breast cancer dangerous to the patient? Cancer, *7*:774, 1954.
51. Ross, D. E.: Cancer of the pancreas: A plea for total pancreatectomy. Amer. J. Surg., *87*:20, 1954.
52. Segi, M., et al.: Cancer Mortality for Selected Sites in 24 Countries, No. 5, 1964–1965. Sendai, Japan, Department of Public Health, Tohoku University School of Medicine, 1969.
53. Silberberg, E., and Holleb, A. I.: Cancer Statistics 1974. Cancer, *24*:7, 1974.
54. Smith, R.: Long-term survival after pancreatectomy for cancer. Brit. J. Surg., *44*:294, 1956.
55. Sommers, S. C., et al.: Pancreatic duct hyperplasia and cancer. Gastroenterology, *27*:629, 1954.
56. Sproul, E. E.: Carcinoma and venous thrombosis: A frequency of association of carcinoma of the body or tail of the pancreas with multiple venous thrombosis. Amer. J. Cancer, *34*:566, 1938.
57. von Schreeb, T., et al.: Renal adenocarcinoma. Is there a risk of spreading tumor cells in diagnostic puncture? Scand. J. Urol. Nephrol., *3*:270, 1967.
58. Walker, R. J.: The diagnosis of carcinoma of the pancreas. J. Roy. Coll. Surg. Edinb., *15*:185, July 1970.
59. Warren, K. W., et al.: A long-term appraisal of pancreaticoduodenal resection for periampullary carcinoma. Ann. Surg., *155*:652, 1962.
60. Warren, K. W., et al.: Diagnosis and surgical treatment of carcinoma of the pancreas. Current problems in Surgery, June 1968.
61. Warren, K. W., et al.: Pancreaticoduodenectomy for periampullary cancer. SURG. CLIN. N. AMER., *47*:639, 1967.
62. Warren, K. W., and Jefferson, M. F.: Carcinoma of the exocrine pancreas. *In* Carey, L. C., ed.: The Pancreas. St. Louis, C. V. Mosby Co., 1973, p. 267.
63. Waugh, J. M., and Gilberson, R. G.: Radical pancreaticoduodenectomy for malignant lesions: Operative technique and pre and postoperative care; Analysis of 85 cases. Proc. Third National Cancer Conf., Am. Cancer Soc., Inc., Philadelphia, J. B. Lippincott Co., 1957.

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The Pancreas in Infants and Children

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With the probable exception of pancreatitis in the alcoholic, all the lesions of the pancreas which are seen in adults occur also in infants and children. However, their frequency, mode of clinical presentation, and treatment tend to be substantially different in children and the differential diagnosis of their clinical manifestations likewise differs.

ANNULAR PANCREAS

Duodenal obstruction due to annular pancreas may occur at any time in life. Why an annular pancreas which has been present from intrauterine life should cause duodenal obstruction for the first time in a man of 40 or 50 is not at all clear, but the evidence would suggest that it is due to inflammatory changes in the pancreatic ring, producing progressive obstruction. In the infant, the obstruction may occur from the moment of birth because of the frequent association of an intrinsic duodenal obstruction—atresia—or at any time in the first weeks or months because of the extrinsic compression of the duodenum by the pancreatic ring.

The generally accepted embryologic explanation for malformation depends upon the development of the pancreas from two anlagen, dorsal and ventral, making their appearance as buds in the mid gut of the 3 or 4 mm embryo before rotation of the gut takes place. In the course of development, the dorsal anlage usually forms the body and tail of the pancreas and part of the head and uncinate process. The ventral anlage consists of right and left portions. The left atrophies early, the remainder contributes to the head of the pancreas, its duct joining with the distal portion of the dorsal duct to form the duct of Wirsung. The proximal portion of the dorsal duct becomes the accessory duct of Santorini. It is postulated that, in rotation of the duodenum, pancreatic tissue from the ventral anlage may be carried within the second portion of the duodenum, subsequently fusing its free end superiorly to the pan-

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creas creating the annular deformity. By 1967, Peiper and Muller-Heubach[10] had found a total of almost 340 well documented cases in the literature.

The width of the pancreatic ring varies from 0.8 to 5.0 cm and it lies almost invariably proximal to the level of the papilla of Vater. In all, some 85 per cent of the instances are in the second portion of the duodenum with the others scattered in the first portion or the third. In autopsy specimens, there is generally a recognizable duct within the ring. Of critical importance in determining clinical management is the fact that the pancreatic tissue is generally firmly attached to, and grown into, the duodenal musculature.[9] A portion of the pancreatic ring is therefore in fact intramural. There is usually a modest amount of hypertrophy of the duodenal wall proximal to the obstruction. Half the reported instances were manifested in the first year of life, and of those, two thirds were symptomatic in the first week of life.

It has recently become clear that an intrinsic duodenal obstruction is a frequent part of the picture.[6] In some instances, this is probably due to the inhibiting effect of the ring of pancreas upon the growth of the duodenum, causing what amounts to a functional duodenal stenosis. Duodenal atresia at this same level may be explainable on the same basis. As in other forms of high intestinal obstruction in the newborn infant, the interference with ingestion by the fetus of the amniotic fluid, and the resultant interference with the dynamics of this fluid exchange, frequently results in hydramnios. Mongolism—Down's syndrome—is not as common as in isolated duodenal atresia, but still occurs with significant frequency. Nonrotation of the intestine, or incomplete rotation, is common, and preduodenal portal vein has been reported as well. Other anomalies of the gastrointestinal tract occur with significant frequency. The implication is of a genuine embryologic malformation as opposed to the situation in intestinal atresia, currently seen to be due to a localized intrauterine vascular accident in the advanced embryo, and generally unassociated with malformation elsewhere in the fetus.[11]

Symptoms

Vomiting is the principal symptom and the onset and severity depend upon whether there is an associated complete obstruction or not. In the newborn infant annular pancreas presents as a duodenal obstruction. Radiologically, a sharp, smooth transverse cut-off in the second portion of the duodenum may suggest annular pancreas rather than duodenal atresia. Both may show the classical double-bubble sign. The presence or absence of air in the rest of the gastrointestinal tract depends upon whether there is an associated duodenal atresia as well.

While the diagnosis can be suspected by the radiologic character of the duodenal obstruction, the precise differential diagnosis is of only academic importance since all forms of duodenal obstruction in the newborn infant require urgent operative relief. The causes of duodenal obstruction include annular pancreas, duodenal stenosis or atresia, compression of the duodenum by "Ladd's bands" in nonrotation or malrotation, volvulus in association with failure of rotation presenting

as a high intestinal obstruction, and rare lesions such as obstruction by duodenal enteric cyst.

Pyloric stenosis generally is of later onset. The vomiting is projectile, the pyloric tumor is palpable, and the duodenum is not dilated, so that there should not be any difficulty in this differential diagnosis.

Operation

As in any laparotomy in the newborn infant, our preference is for a transverse incision, in this instance in the upper abdomen. An annular pancreas is readily recognizable as a band of pinkish white tissue traversing, and fixed to, the duodenum. The temptation to divide the pancreatic ring is to be avoided. It would be difficult because of the intramural location of a substantial portion of the pancreatic tissue, and hazardous because of the usual presence of the significant duct within it,[7] division of which has led to escape of pancreatic fluid and pancreatitis, either with disastrous immediate results, or with a resultant "recurrence" from fibrosis caused by postoperative pancreatitis. Further, the frequent association of an intrinsic obstruction of the duodenum counsels a by-pass operation rather than the apparently simple maneuver of division of the ring. The preferred operation is either duodenoduodenostomy or duodenojejunostomy by the retrocolic route. Gastrojejunostomy should obviously be avoided. The literature in the early years of this century when gastroenterostomy was the regularly employed treatment for pyloric stenosis contains descriptions of the early appearance of anastomotic ulcers in such patients.

PANCREATITIS

The chief cause of pancreatitis in children in this country is trauma. The salient feature of such traumatic pancreatitis in children is the frequency with which the trauma is relatively minimal. A trifling fall upon a toy or the poking of a tricycle handlebar into the epigastrium has been sufficient to cause a pancreatic injury and pancreatitis.[4, 15] Classically, the initial symptoms are mild. All too often children are seen in the emergency room and sent home, or admitted to the hospital for observation for a day or two and found to have only minimal abdominal tenderness which recedes, allowing them to be discharged. The development of a pseudocyst or of pancreatic ascites in the subsequent days or weeks finally establishes the diagnosis.

Despite the common delay in diagnosis of traumatic pancreatitis in children, and the even slower recognition of pseudocyst in the pancreas in children than in adults, the ultimate results of treatment are good and superior to those in adults. It is one of the beauties of pediatric surgery that ordinarily one is dealing with an organism healthy in all respects but for the lesion which has attracted attention, and in children with traumatic pancreatitis and pancreatic cyst, there is no underlying preexisting disease of the pancreas or biliary tract, and the heart, lungs, kidneys and liver have not yet had to stand the vicissitudes of several

decades of the wear and tear of ingested and inhaled noxious materials, bacterial disease, and the inexorable passage of time.

The lesion in traumatic injury to the pancreas in children is almost invariably a vertical transection of the pancreas, directly over the vertebral column, and therefore usually somewhat to the left of the superior mesenteric vessels. In almost every reported case, except those in association with massive automobile injury, the injury to the pancreas is isolated. Any child with genuine abdominal tenderness after an injury merits serious consideration for abdominal exploration. A transection of the pancreas and for that matter a rupture of the jejunum, may give remarkably and deceptively few symptoms for one to several days. With injury of the pancreas, films of the abdomen may ultimately show a retroperitoneal mass displacing the stomach forward or the colon downward or both. Because the injury is to the body or tail of the pancreas, the C-loop of the duodenum, initially at least, is usually not much displaced and the reversed 3-sign only occasionally seen. The diagnosis is made on the presence of abdominal tenderness and the finding of an elevated serum amylase. If abdominal aspiration, so frequently resorted to for blunt force abdominal injury, yields fluid, an amylase determination should be made.

Treatment

The treatment of acute traumatic pancreatitis caused by subcutaneous injury of the abdomen is immediate operation. If the transection of the pancreas is obvious, the portion of the pancreas distal to the line of rupture is resected. So long as the splenic artery is spared, the distal portion of the pancreas may be removed with the attached splenic vein and the spleen spared, the short gastric vessels providing adequate venous collateral. If operation has been delayed for several days, there is frequently so thin-walled a pseudocyst as to constitute no more than a localized intra-abdominal collection of fluid. In such instances, internal drainage of the cyst into a Roux-Y jejunal loop is not feasible. At this point, the edema, hemorrhage and exudate argue against an attempt at definitive resection of the distal pancreas. In such instances, the fluid is aspirated and a sump drain placed down to the injured pancreas. In most instances, drainage will ultimately cease, and after an appropriate sinogram to demonstrate that no cavity persists, the drain may be withdrawn. If a pancreatic fistula persists for a long time, one has the alternative ultimately, either of resecting the distal portion of the pancreas, or of implanting the sinus tract, with a button of abdominal skin, into the stomach or a Roux-Y loop.

In patients who are recognized late as having a pseudocyst, in whom the cyst has a well developed wall, my preference is for a Roux-en-Y cystojejunostomy. The reported results with cystogastrostomy seem equally good. The cyst may be so enormous as to fill the abdomen, and contain several liters of fluid, or may be relatively small and attached to the tail or body of the pancreas in such a way as to invite successful resection of the cyst with the attached portion of pancreas. Once a mature cyst is encountered, simple drainage has no place.

A few pseudocysts have been reported in children with no history or evidence of trauma, and pseudocysts have occurred in children after mumps pancreatitis, and after acute hemorrhagic pancreatitis without obvious cause. Acute pancreatitis with or without ultimate development of a pseudocyst has been reported from a number of institutions without any suspicion of trauma and without any demonstrated etiology. Acute suppurative or hemorrhagic pancreatitis has occurred as a complication of sepsis, either generalized or apparently localized elsewhere in the body.

The transformation of physicians and pediatricians into aggressive therapists has permitted them to abort, modify, and cure many conditions once beyond the realm of treatment, or previously amenable only to operative treatment. A constellation of iatrogenic diseases has made its appearance as a result. The widespread use of steroids in substantial doses and for long periods of time in children with nephrosis, ulcerative colitis, renal transplants, and other conditions has produced a significant number of cases of pancreatitis. Steriod-induced pancreatitis may vary from a mild disease with abdominal pain and elevated serum amylase to a fulminating hemorrhagic pancreatitis destroying the pancreas, producing widespread fat necroses and resulting in collapse and death within a few days. The mechanism of steroid-induced pancreatitis is not understood. The treatment is operative if the patient's condition is deteriorating, if abscess or a widespread necrosis of the pancreas or pseudocyst are suspected or if pancreatic ascites occurs. The chlorothiazide diuretics have occasionally been known to cause pancreatitis, and there is every reason to suppose that as time goes on and the list of potent drugs to which patients are exposed increases, other drugs will be found to cause pancreatitis.

A form of recurrent pancreatitis occurs in children, sometimes severe and sometimes mild, with a high familial incidence and associated with aminoaciduria or hyperlipemia or both. Extensive calcification of the pancreas sometimes results. Chronic recurrent pancreatitis, not familial, and without an obvious basis, has also been reported.[16]

In the majority of children with pancreatitis once the inciting mechanisms have been corrected and the complications remedied, there is no further trouble: however, a few patients have had repeated attacks in the absence of any disease process or drug exposure that could be considered causative.

HYPOGLYCEMIA IN INFANCY AND CHILDHOOD

In the first 6 months of life, at a time when the brain with its enormous need for glucose is growing rapidly, periods of profound hypoglycemia may have devastating and permanent effects upon the central nervous system. In the older child, islet cell adenomas, glycogen storage disease, pituitary and adrenal insufficiency states, malabsorption, galactosemia, and extrapancreatic tumors producing insulin may cause symptomatic hypoglycemia. In the newborn infant, in addition, there is

the symptomatic hypoglycemia seen in infants born of toxemic mothers, of diabetic mothers, and of mothers with prediabetes and gestational diabetes; hypoglycemia is also seen in dysmature infants ("small for dates", "birth weight low for length of gestation"), in infants with severe erythroblastosis, and, in the largest group of all, in infants with idiopathic or agnogenic hypoglycemia.

Hypoglycemic infants attract attention by their pallor or jitteriness, respiratory irregularities, collapse, or convulsions. In older children, as in adults, personality and mental changes may be observed before more severe signs are manifested. The hypoglycemia may be mild and self-limited in all the conditions listed, except islet cell adenoma and agnogenic hypoglycemia, and, as well, when associated with glycogen storage disease or pituitary or adrenal disorders. There is evidence, however, that even the transitory hypoglycemia in dysmature infants and the infants of mothers with complicated pregnancies may be associated with mental retardation and spasticity, so that even in these milder forms, a vigorous therapeutic attitude is required. There are no valid data to show what level of hypoglycemia can be tolerated by an infant, or how many episodes or episodes of what duration without danger of permanent damage, and this fact is basic to the aggressive attitude we take toward the problem.

In neonates and infants under 6 months of age, the only safe attitude to take is that any episode of hypoglycemia is dangerous, that effective therapy must be instituted at once, and that to be effective, therapy must prevent hypoglycemia as well as the recognizable clinical manifestations of hypoglycemia. If treatment is not promptly successful or if symptoms recur when treatment is withdrawn, operation upon the pancreas should be undertaken. It is my contention that there is less hazard in this approach than in continuing high risk efforts at avoiding operation with, for instance, high doses of steroids. Operative treatment is likely to find and cure most islet cell adenomas, and these have been reported even in the newborn infants. Subtotal or all but total pancreatectomy will relieve hypoglycemia in a substantial proportion of instances of agnogenic hyperinsulinism. Children operated upon at a few weeks of life and cured by all but total pancreatectomy for diffuse islet cell hyperplasia have turned out to have been already damaged by the prolonged and severe hypoglycemia during the unsuccessful attempts at nonoperative regulation.[11, 13]

A review of the still not large literature on agnogenic and leucine sensitivity hypoglycemia from the standpoint of the utility and timing of the 85 per cent pancreatectomy leads to the following observations: The operation is remarkably easy, the mortality and morbidity have been extremely low, postoperative pancreatitis has rarely occurred, and, as we have indicated earlier, the spleen need not be sacrificed. With an 85 per cent pancreatectomy, diabetes occurs uncommonly. Of substantial significance is the fact that in nearly every series of children operated upon for these conditions, some children thought to have had idiopathic hypoglycemia in fact proved to have islet cell adenomas. It is our view that diagnostic tests are not as yet adequately specific to pinpoint the nature of a

given hypoglycemia. I have such respect for the high incidence of mental retardation, convulsive disorders, and spasticity in children who have a hypoglycemic disorder in infancy that I feel this grave penalty for the delay in cure warrants a surgical policy sufficiently vigorous so that some infants may be operated upon who might, in fact, not have required pancreatectomy for ultimate relief.

Since these children will not be diabetic, since splenectomy is not required, since the risk of operation is not great, we urge operation on all otherwise normal infants whose hypoglycemia cannot be controlled by acceptable nonoperative measures, without repeated escape. We do not consider long-term steroid therapy an acceptable method of treatment as an alternative to operation, and if a steroid treatment-induced remission is followed by relapse, operation should be undertaken promptly.

The pancreatectomy which we perform is an 85 per cent to 90 per cent resection, leaving only a portion of the head. To do less is to invite failure of relief of the hypoglycemia. If hypoglycemia continues after such resection, total pancreatectomy is required and has been performed with good results although diabetes inevitably occurs. In the 85 per cent pancreatectomy, blood sugar is high immediately after operation and several doses of insulin may be required, but blood sugars are down to normal levels in 3 or 4 days.

ISLET CELL TUMORS

Not very long ago, islet cell tumors were thought to be rare in childhood and never found in the neonate. An increasing number of reports now have corrected this misconception.[2, 3, 5] Diagnosis in older children is made in the presence of profound starvation-induced hypoglycemia and elevated serum insulin levels. The tumor may not only be diagnosed but localized by arteriographic demonstration but, thus far, not in an infant.

Our preferred approach is through a transverse upper abdominal incision, gaining access to the pancreas through the gastrocolic omentum. As in adults, if the tumor has not been demonstrated arteriographically and is not grossly visible or palpable at operation, partial pancreatectomy is undertaken and a thin slice gross section performed by the pathologist in the operating room until the adenoma is found or an 85 per cent pancreatectomy has been performed. Before such a "blind" resection is begun, both surfaces of the tail and body of the pancreas and as much of the head as possible are carefully viewed and palpated. While the adenomas are occasionally multiple, the cure rate will be high once a single adenoma is found and one should desist at that point, extending the pancreatectomy in a second operation if symptoms persist or recur.

The operation is well tolerated—in most series no deaths are reported, insulin is required only briefly and diabetes is not produced. Cyanosis, apneic spells, and convulsions have been recorded at 3 hours of life, at 2 hours with blood sugar or less than 19 mg per 100 ml, at 20

hours and on the second day with glucose levels of 5 mg per 100 ml. Tremulousness at birth with symptoms progressing to convulsions at 20 hours and on the third day of life have also been reported. The Australian report of operation performed on the nineteenth day of life[12] probably represents the earliest on record.

One does not often think of carcinoma of the pancreas in infants and children and it is indeed rare. Something over 30 cases of malignant tumors of the pancreas in children may have been reported.[11]

Nonfunctioning malignant islet cell tumors are the single most common group of malignant tumors of the pancreas in children. A single such tumor produced hypoglycemia.[8] The youngest patient reported to have had a carcinoma of the pancreas is a 3 month old infant,[14] who presented with abdominal enlargement and a palpable mass. At laparotomy, he was found to have an enlarged liver with numerous metastatic nodules and autopsy disclosed tumor of the head and body of the pancreas.

At least nine children have had radical pancreatectomies for cancer.[11] The most common single presenting symptom has been an abdominal mass, with jaundice occurring in less than a third, bleeding in a few, and diarrhea in about a quarter of the patients. Abdominal pain was relatively uncommon. The diarrhea, which was common and was frequently troublesome, suggests the possibility that some of these were actually non-islet cell carcinomas of the Zollinger-Ellison type.

Of the 9 pancreaticoduodenectomies which we have been able to find, Becker's[1] patient was the youngest, operated upon at 15 months and surviving for 3 years, ultimately dying of recurrence. There would appear to have been a certain selectivity in case reporting since none of the patients reported died of the operation. No child with carcinoma of the pancreas has survived without pancreaticoduodenectomy and all of those reported were in good health at the time of the original report from a few months to 6 years after operation, and one 16 years after operation.

Pancreaticoduodenectomy in children has been demonstrated not to result in any interference with growth or development. The indication is clear that an apparently malignant tumor of the pancreas in a child should be treated by radical resection with the exception that the mortality will be lower and the cure rate higher than with the oridinary adenocarcinoma of the pancreas in adults.

REFERENCES

1. Becker, W. F.: Pancreatoduodenectomy for carcinoma of the pancreas in an infant: report of a case. Southern Surgical Association, Boca Raton, Florida, Dec. 5, 1956.
2. Buist, N. R. M., Campbell, J. R., and Castro, A.: Congenital islet cell adenoma causing hypoglycemia in a newborn. Pediatrics, 47:605, 1971.
3. Drash, A., and Schultz, R.: Islet cell adenoma in childhood: report of a case. Pediatrics, 39:59, 1967.
4. Fraser, G. C.: "Handlebar" injury of the pancreas. J. Pediat. Surg., 4:216, 1969.
5. Grant, D. B., and Barbor, P. R. H.: Islet cell tumor causing hypoglycaemia in a newborn infant. Arch. Dis. Child., 45:434, 1970.

6. Hays, D. M., Greaney, E. M., Jr., and Hill, J. T.: Annular pancreas as a cause of acute neonatal duodenal obstruction. Ann. Surg., *153*:103, 1961.
7. Heymann, R. L., and Whelan, T. J., Jr.: Annular pancreas: Demonstration of the annular duct on cholangiography. Ann. Surg., *165*:3, 1967.
8. Hurez, A., Bedouelle, J., Debray, H., et al.: Carcinome Langerhansien avec manifestations hypoglycemiques severes chez un enfant de 9 ans—pancréatectomie partielle. Arch. Fr. Pediat., *18*:625, 1961.
9. Hyden, W. H.: The true nature of annular pancreas. Ann. Surg., *157*:1, 1963.
10. Peiper, H. J., and Müller-Heubach, E.: Das Pankreas anulare und seine chirurgische Behandlung. Langenbecks Arch. Klin. Chir. *320*:322, 1968.
11. Ravitch, M. M.: Anomalies of the pancreas and Lesions of the pancreas in infancy and childhood. *In* Carey, L. C., ed.: The Pancras. C. V. Mosby Co., St. Louis, Mo. 1973.
12. Robinson, M. J., Clarke, A. M., Gold, H., et al.: Islet cell adenoma in the newborn: report of two patients. Pediatrics, *48*:232, 1971.
13. Schwartz, J. F., and Zwiren, G. T.: Islet cell adenomatosis and adenoma in an infant. J. Pediat., 70:232, 1971.
14. Stein, M. D., et al.: Carcinoma of the pancreas in the infant. Presentation of a case. Pediat. Prat. (Ger.), 33:75, 1962.
15. Weitzman, J. J., and Swenson, O.: Trautmatic rupture of the pancreas in a toddler. Surgery, 57:309, 1965.
16. Williams, T. E., Jr., Sherman, N. J., and Clatworthy, H. W.: Chronic fibrosing pancreatitis in childhood: a cause of recurrent abdominal pain. Pediatrics, *40*:119, 1967.

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Hepatic Trauma in Adults

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Trauma is endemic in the United States and in many other motorized and urbanized countries. In the 15 to 40 year age group of promising and productive human beings, it is the leading cause of death. Furthermore, the economical drain imposed on the community by post-traumatic morbidity and the need for rehabilitation—in those who survive—is colossal. Until the recent, Aramco-sponsored speed limits, vehicular accidents were increasing each year, resulting in blunt injuries to the chest and abdomen. Penetrating injuries are still rising steadily, paralleling a general rise in the crime rate, mostly in our large metropolitan conglomerations.

Of all blunt, abdominal injuries some 15 to 20 per cent involve the liver, the largest friable organ in the body.[27] Penetrating wounds of the abdomen result in injury to the liver more frequently (24 per cent) than to any other intra-abdominal organ, in spite of its protected location within the rib cage.[42]

While the expertise to prevent death from accidents and to limit the physiologic impact of injury exists today, the ability to deliver all component parts of this expertise lacks in most communities. Until such time as specialized, nationally integrated two-way communication systems, mobile intensive care ambulances staffed by highly-trained technicians, and categorization and regionalization of hospital emergency departments make possible a national assault on the epidemic of trauma, individual surgeons will be faced sporadically with the management of minor and major traumatic conditions. Among these, injuries to the liver may be the easiest or the most challenging problems any surgeon will ever have to face.

TYPE AND EXTENT OF LIVER INJURIES

The type and extent of a liver wound depends on the offending agent, as well as the anatomic area and force of penetration or impact at the time of injury.

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Penetrating wounds are due to stabbings or missiles. More serious and fortunately rare variations of these types are impalement on a pointed object such as a spiked fence and penetration by a blunt object such as shrapnel in wartime, heavy and sizable metal objects in industrial accidents,[29] and the entire bolus of a shotgun discharge at close range in hunting and accidents of brotherly love.

In general, stab wounds are relatively clean, incised wounds of the liver parenchyma causing bleeding and bile leakage, but only minimal tissue damage. They may vary, however, from an icepick wound—not unlike a needle biopsy of the liver—to a complete transfixion of the organ by a long butcher knife.

In missile wounds, especially those caused by high velocity projectiles, the site of entrance and exit belie the potential severity of intrahepatic vascular, bile duct, and especially parenchymal damage. Tissue destruction along the missile tract, although more limited, is similar to that obtained in liver lacerations caused by blunt injuries. In gunshot wounds, the severity of tissue destruction increases with the volume and velocity of the bullet. The liver may literally explode under the impact of large, blunt projectiles or of high-velocity bullets discharged at close range.

Blunt injuries to the liver cause the most serious derangements of any hepatic wounds, all other criteria such as depth of penetration and anatomic location being equal. A fracture of liver capsule and parenchyma, more often of the larger right lobe, extending irregularly into the lobe sometimes to the point of amputation, is the usual result of severe blunt trauma such as in steering wheel or abdominal seat belt (falsely applied) contusions. Blood vessels and bile ducts are lacerated along the irregular and fjord-like extensions of the laceration. Large masses of liver tissue are contused and necrose as a result of both the direct injury and the impaired blood supply. More rarely, the liver may "burst" centrally, leaving peripheral organ and capsule intact. The external appearance of the liver at the time of exploration may be very deceiving and the extent of damage is often appreciated only secondarily by the patient's poor clinical response, progressive jaundice, the severe derangement in enzymes and liver function tests, and the occurrence of a dreaded secondary complication such as hemobilia, deep or subcapsular infection or peripheral dissection of the hematoma with rupture of Glisson's capsule and secondary intraperitoneal hemorrhage.

A primary subcapsular hematoma with a limited liver fracture below the intact capsule is rare in blunt trauma to the liver. The original episode may be trivial and go unnoticed,[24] as in the instance of a college coed who fell during graduation potato sac races and suffered a short moment of dizziness. Three months later shock, jaundice, and high fever developed and she complained of severe abdominal pain. Exploration showed a complete elevation of Glisson's capsule by a liquid hematoma and rupture of it over the left lobe. The original liver injury was not apparent. In general however, secondary ruptures of the capsule occur within 24 to 48 hours following injury.[24]

The *extent* of a given liver injury may be difficult to assess, since its

true limits are hidden in the depth and width of liver parenchyma, obscured by the presence of clotted blood. Anatomically, the liver cannot be inspected completely and the original limited exploratory incision may further contribute to this frustration. Finally, the attention of the surgical team is often held by other equally serious problems within the abdomen or across the diaphragm in the chest and mediastinum. Yet, the surgeon's final decision is based on the clear-cut knowledge that the injury is limited to the periphery, extends into or arises originally from the central portions of the liver, or involves the hepatic hilus. A problem of special and critical importance is the identification of injuries to the hepatic veins in blunt trauma and to the inferior vena cava in penetrating trauma.

PREOPERATIVE MANAGEMENT

Diagnosis and Operative Indications

In fully one third of all patients admitted to a busy emergency department with penetrating or blunt abdominal trauma, urgent laparotomy is *mandatory* because of shock (not explained by extra-abdominal injuries), gastrointestinal bleeding (nasogastric tube, rectal digital examination), free intraperitoneal air, hematuria, and evisceration. Because of the location of a penetrating wound, or the location of pain, tenderness and guarding in the right upper quadrant in blunt injuries, involvement of the liver is strongly suspected preoperatively.

In the less critically ill patients, the preoperative approach can be one of *deliberate* haste. The mere presence of a penetrating wound is not an absolute indication for exploration. Intraperitoneal involvement is determined by sinograms of the wound or by findings of pain, localized or generalized tenderness, rebound tenderness, guarding and absent or diminishing bowel sounds. These same findings are those used in the examination and evaluation of the abdomen in blunt trauma. Repeated examinations by the same surgeon are of the utmost importance in equivocal cases. Again, the suspicion of liver injury is based upon the localization of penetration and/or clinical findings.

In these patients, the initial *hematocrit* is helpful only as a baseline. If time permits, the serial documentation of a falling hematocrit (within 1½ to 2 hours after injury) will point to active intra-abdominal bleeding in the absence of any other known source of hemorrhage. Enzymes and liver function tests are useful only in the neglected or misdiagnosed liver injury at a time of progessive parenchymal damage or post-traumatic complication.

Abdominal paracentesis is most helpful in the detection of hemoperitoneum, such as a liver injury may produce. We find it very useful in the patient with minimal, equivocal physical findings and where associated head trauma or lower rib cage contusion makes interpretation of the abdominal findings difficult. In most instances, however, paracentesis and lavage will confirm the presence of rather convincing clinical

signs or support continued observation in the absence of clinical signs of serious injury. A No. 16 Intracath needle is inserted into the center of one or all four quadrants, beginning with the one where clinical signs are most intense. When a "give" is felt, the needle has entered the peritoneal cavity and the plastic catheter is advanced.[46] If it moves freely, this is one further sign of penetration into the open peritoneal cavity and the needle is withdrawn. Blood or bile may then return spontaneously or be aspirated. If this positive result is obtained, the procedure is terminated. If none of the four quadrant taps is positive, the catheters are left in place for continued monitoring. Irrigation of the abdomen with 1000 cc of Ringer's lactate and aspiration of the fluid is used in patients with negative paracentesis.[37, 47, 48] This procedure may be repeated. Caution should be exercised in the patient who has undergone previous abdominal operation. The accidental penetration of a viscus, however, has had no serious consequences. Paracentesis should be performed only after radiographic examination of the chest and abdomen. We have explored two patients with the "mandatory" indication of free peritoneal air, in whom the air was introduced by precipitous paracentesis.

Sinograms, mostly of stab wounds of the abdomen, are performed by cleaning and draping the wound of entrance. Under local anesthesia a purse-string suture of 2–0 silk is placed around the wound. A No. 12 or 14 French rubber catheter is then advanced into the wound and the purse-string is tightened. An Intracath is used at times for small stiletto wounds. Sixty to 80 cc of Hypaque 50 per cent, containing 1 cc of Methylene Blue, are injected under pressure into the catheter; the quantity should be sufficient to produce a slight bulge of the skin surrounding the wound. The Methylene Blue is added to detect leakage to the outside. After injection, the catheter is clamped and the patient is tilted on the x-ray table from side to side and up and down. Films are taken in the anteroposterior and lateral and oblique positions. Scout films should be taken prior to the Hypaque injection. By using this technique, the rate of unnecessary abdominal explorations is reduced from some 50 per cent to 15.9 per cent.[43] Patients that do not have intraperitoneal penetration are sent home after 24 hours of in-hospital observation.

We have also used the *selective, clinical approach* of Shaftan: quadrant or generalized pain and tenderness, rebound tenderness, guarding, and absent or diminishing bowel sounds.[40] By basing the indications for laparotomy on these clinical findings in those patients that do not have mandatory signs for exploration, the percentage of unnecessary laparotomies in the hands of experienced observers is even lower, some 7.3 per cent.[43] A somewhat longer observation period from 48 to 72 hours is required, after initial negative clinical findings have been confirmed by repeated examinations.

Angiography is rarely indicated during the early, acute phase of trauma because a diagnosis should be established in the vast majority of patients by piecing together the total clinical picture. Furthermore, it should be stated that in trauma, as in so many other disease conditions, it has become too easy to dream up and perform yet another

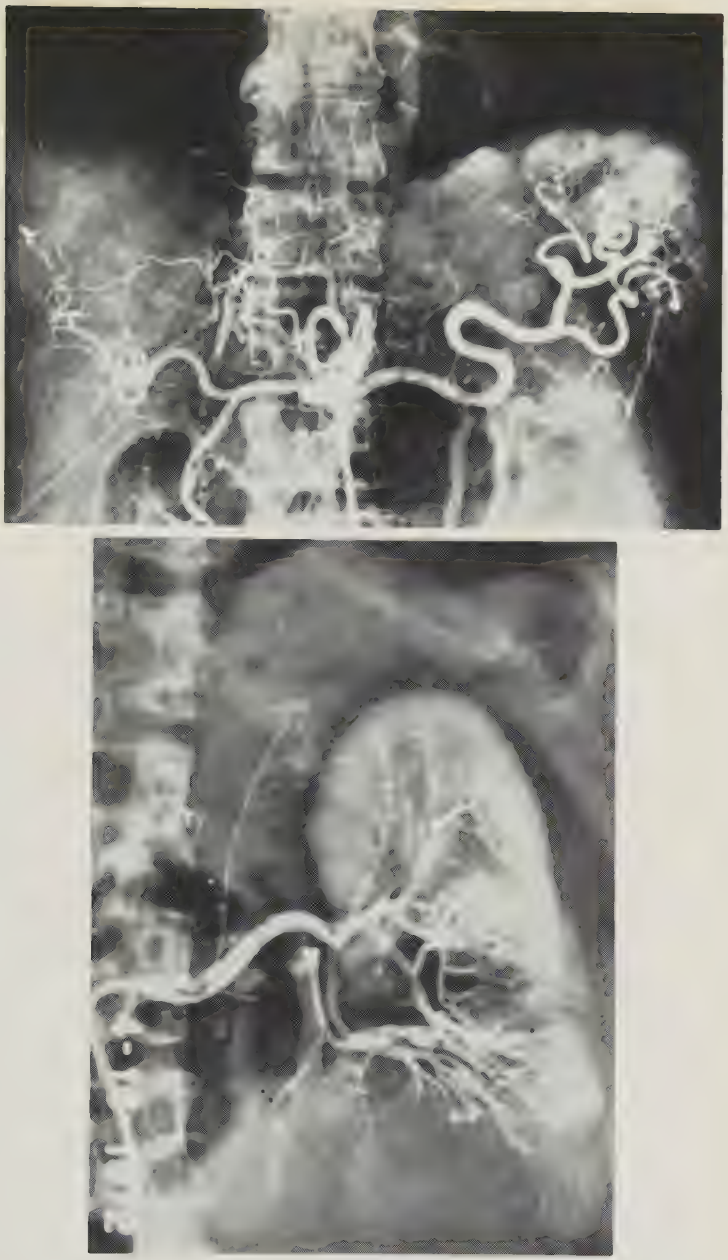

Figure 1. Celiac and left renal arteriograms on 59 year old patient involved in head-on collision. There were fractures of the left scapula and left ribs 2–7, left pneumothorax and hematuria. I.V.P. showed good function bilaterally with extravasation on the left. Because of left upper quadrant tenderness and a suspected rupture of the spleen in a patient with much left lower rib cage symptoms, a celiac arteriogram was done. Extravasation of contrast material within the parenchyma of the liver seen at the level of the second lumbar vertebra was a completely unexpected finding. A normal spleen was found. The rupture of the lower pole of the kidney was confirmed. During all of this the patient's condition remained quite stable, the hematuria stopped, his blood pressure did not rise and repeat I.V.P. showed good function bilaterally without extravasation. (Arteriogram by Dr. M. Boehnke.)

paraclinical examination, when speedy treatment based on a rational analysis of all the clinical findings is usually in the best interest of the patient and of medical economics. This does not detract from the fact that arteriography is helpful in patients that are stable and are suspected to have a liver injury,[1, 2, 8] obscured perhaps by head trauma or by a central location of the liver laceration. In such patients it will also be possible to examine by aortography[14] hidden lacerations of the spleen, kidneys, and mesentery (Fig. 1). Selective arteriography on the other hand is the best single diagnostic tool in the chronic phase of liver trauma when hemobilia, subcapsular hematoma, and intrahepatic abscess are suspected.[1, 8]

Liver scan is not a useful diagnostic modality in acute liver trauma, because of the time involved and the unreliable results obtained with liver scan in general.[47] However, Richie and Fonkelsrud have used this technique in four patients with subcapsular hematoma for diagnosis and nonoperative follow up.[36] Serial scans are interesting in patients with hepatic resection to document liver regeneration.

Preoperative Therapy and Monitoring

Patients that are unresponsive and in deep clinical shock on arrival to the emergency department, with a serious liver injury, often associated with other life-threatening insults, have a grave but by no means hopeless prognosis. A valiant attempt at respiratory and cardiac resuscitation should always be made and the need for early transfer to the operating room should be recognized promptly. Emergency operation with hemostasis may be the most essential part of the treatment of hemorrhagic shock.[4, 13, 26, 44, 47]

In all patients with suspected liver trauma a large bore intravenous portal is established in an upper extremity, preferably via the subclavian vein. Blood is drawn for type and crossmatch as well as baseline hematocrit, and volume is restored by the administration of Ringer's lactate or normal saline. In patients with threatening vital signs the efficacy of volume replacement is monitored by central venous pressure and by urinary output and specific gravity after introduction of a Foley catheter. Blood, if needed, is administered as soon as it becomes available. All indicated drugs are administered intravenously (preferably not via the CVP line). Hepatotoxic drugs should be avoided. Broad spectrum antibiotics are commenced at this stage and should be continued intra- and postoperatively. A naso-gastric tube is passed, in unconscious patients only after the trachea has been shielded by a cuffed intratracheal tube. Serial hematocrits and paraclinical examinations, as described in the section on diagnosis, are performed only if the added information does not endanger the patient's survival and can be expected to help significantly in the decision making. Most of these steps are best carried out in an operating room where all the necessary equipment and manpower are available away from the distraction of a busy emergency room. In addition, operation can be started while volume replacement is in progress.[4, 13, 26, 44]

If major hepatic trauma is suspected, hypothermia should be ini-

tiated and continued intraoperatively with the goal of lowering the body temperature to 30 to 32° C. Since temporary occlusion of the hepatic vascular inflow is often required in the control of major liver injuries, inflow occlusion under hypothermia can be extended to 1 hour without risk of anoxia and further liver damage.[6, 11]

INTRAOPERATIVE CONDUCT

Incision and Exploration

For suspected liver trauma, the incision should be in the upper midline. The entire thorax should also be prepared so that the incision can be extended into the seventh or eighth intercostal space to the right or in a straight line upward through the sternum. The incision should not be carried through an existing penetrating wound because of the high incidence of severe wound infections in such instances. If it is not possible to avoid a penetrating wound, the latter should be excised first and instruments and gloves should be changed prior to proceeding with the midline incision. While we have used the right intercostal extension in the past, we now do favor the vertical extension sternotomy because it gives excellent access to the inferior vena cava, hepatic veins, and heart, and avoids section of the muscular diaphragm and entrance into the pleural cavity (Fig. 2).[31]

Upon entering the abdomen, all possible injuries should be mentally recorded at a quick glance and priorities in their operative management should be established. Active hemorrhage takes precedence over leakage from perforated viscera.

Obvious parenchymal and hilar injuries are inspected and the liver and surrounding structures are gently palpated about the injury. Hidden or suspected injuries may require division of the ligamentum teres, the falsiform, and/or both triangular ligaments. Exploration of the upper abdomen is greatly facilitated by a self-retaining retractor fixed to the operating table.* In posterior and apical wounds the surgeon's eyes are carried on his gently probing fingertips. Absolute insistence on seeing these wounds by pulling and turning the liver may result in the dislocation of a hematoma that has so far – precariously – tamponaded a laceration of the inferior vena cava or a hepatic vein, before steps for control of such a serious injury can be undertaken. In terminating his evaluation, the surgeon should have clear impressions as to the extent of liver injury: peripheral, central, hilar, subcapsular hematoma with underlying parenchymal tear, hidden intraparenchymal "burst" (the most difficult to diagnose). He should be certain that the inferior vena cava and hepatic veins are or are not involved. He should have evaluated the accumulated and ongoing blood loss and he should formulate a plan for a successful surgical approach to all of the problems at hand.

*Rochard Retractor, Ulrich, St. Gallen, Switzerland

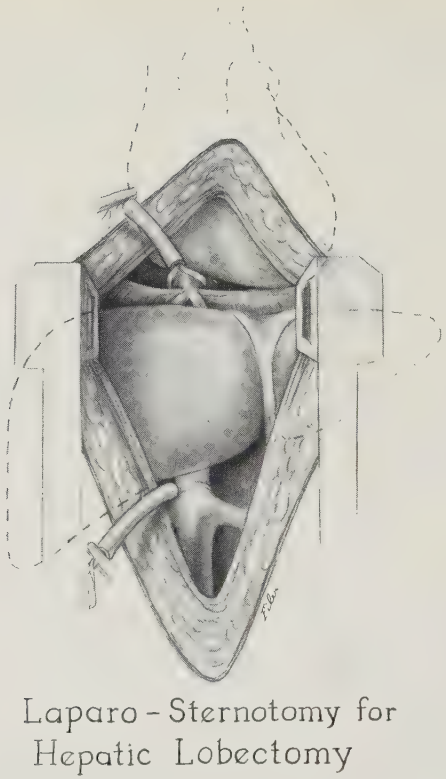

Figure 2. Mediastinotomy extension of upper midline abdominal incision.[31] The wide retraction obtained by this combined incision permits easy access to the lower inferior vena cava and the structures of the porta hepatis. The diaphragm is incised in the midline. It is more tendinous in this area and the anteroposterior distance is much shorter than for any other incision of the diaphragm. The hepatic veins can be exposed without having to pull down the liver and the liver is much more easily mobilized through this incision. The upper inferior vena cava can be approached and isolated by opening the pericardium. If an inferior vena cava bypass shunt is required, the mediastinotomy will give easy access to the atrial appendage. (By permission of Contemporary Surgery, McGraw-Hill, New York.)

SURGICAL TECHNIQUES

By the time operation is undertaken, bleeding from most parenchymal lacerations has either ceased or can be controlled by local compression with Mikulicz pads and aspiration.[3, 12, 47] Clots are evacuated by hand and oozing of fresh blood is aspirated. The treatment of pure parenchymal and hilar lesions depends on the extent of injury.

Conservative and Reconstructive Techniques

Superficial peripheral lacerations, usually due to stab wounds and grazing gunshot wounds, are best treated with drainage. No sutures are taken if there is no bleeding.[20]

Deep peripheral lacerations are managed by horizontal mattress sutures after all identifiable bleeding points have been ligated. Great care is taken to avoid any dead space in the depth of the wound. If

bolsters are used in order to avoid cutting of the sutures into the liver parenchyma, these bolsters should be small pieces of muscle or greater omentum. Gelfoam is a poor material for this since it softens with resulting loosening of the sutures.

Through-and-through wounds of the liver parenchyma, usually due to missiles but also at times to forceful stab wounds with a long knife, represent a special problem in detection, anatomic approach, and surgical management. Very often the wound of entrance or exit is situated posteriorly, superiorly, or in the bare area of the liver. After both wounds have been exposed, blood and bile continues to exude from them at a slow but steady rate. A direct approach to such injuries for debridement and hemostasis is obviously impractical. In this situation we have found suction catheters, introduced through the wound of exit and entrance, of great help.[7, 42] Suction is applied on the operating table and if the oozing of blood and bile from the wounds stops and the aspiration of blood and bile through the catheters is nothing more than a small trickle, then no further operative treatment is instituted. Suction is continued in the postoperative phase until all secretions have stopped and the catheters are then slowly removed. If, however, during the operation suction produces a steady flow of blood, then a large intrahepatic cavity is suspected and is localized by the injection of contrast material through the catheters, and radiographic studies. The cavity is then opened, debridement and hemostasis are performed, or excision of compromised liver is undertaken. Injuries limited to the *gallbladder* are most often due to penetrating agents and are treated by simple cholecystectomy.

Injuries to the *liver hilus* are also due most frequently to penetrating wounds and are relatively easy to diagnose at operation. If the hilar structures are torn by blunt injury, the picture is often one of a complicated upper abdominal catastrophe involving the duodenum and the head of the pancreas. In injuries to the extrahepatic bile ducts from blunt trauma, without vascular, duodenal and pancreatic involvement, the diagnosis at operation was missed in 5 of 6 cases and the clinical picture was unclear in another group of patients where definitive operation was delayed for an average of 3 weeks.[49]

Injuries to the liver hilus may involve the extrahepatic bile ducts, the arterial tree or the portal system, individually or in various combinations. Ideally, anatomic reconstruction should be attempted. In the case of arterial or portal injury, the reconstruction is done with inflow occlusion and under the protection of hypothermia. If there is loss of tissue and the vessel ends cannot be approximated after whatever proximal and distal liberation is feasible, then a Kocher maneuver of the duodenum will provide for minimal added length and will lessen tension on the anastomosis. If the vessel ends still cannot be approximated safely, a vein graft should be used.

Ligation of the portal vein is compatible with survival, and ligation of the hepatic artery, especially proximal to the gastroduodenal artery, may produce only focal hepatic necrosis or may have no serious consequences at all, depending on the collateral hepatic blood supply. Interruption of both the arterial and portal flow is incompatible with life. In

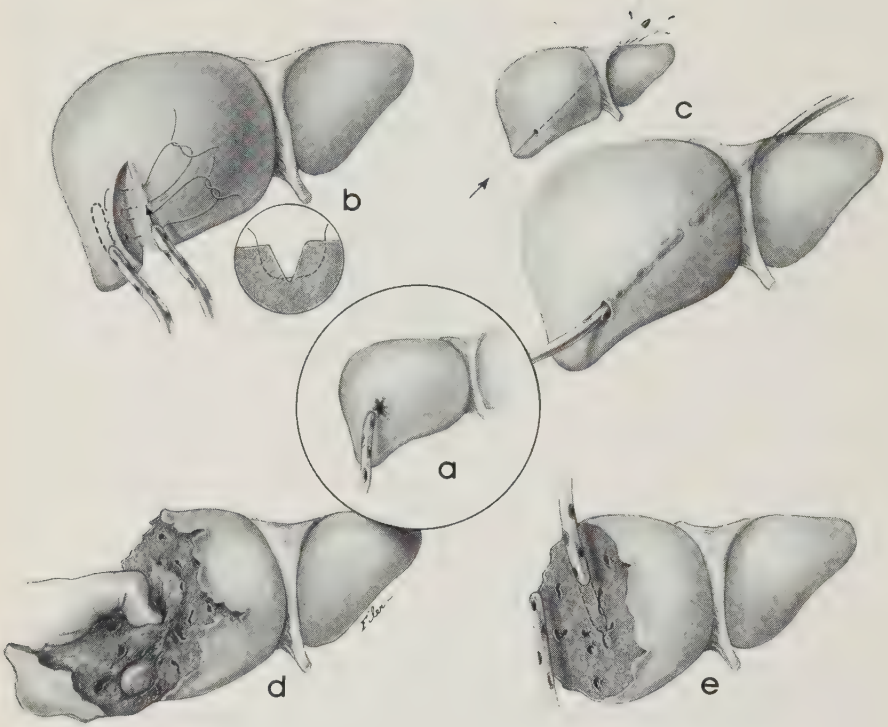

Figure 3. *A, Superficial peripheral lacerations*, usually due to stab wounds, are best drained only. No sutures are taken if there is no bleeding.

B, Deep peripheral lacerations are closed by horizontal mattress sutures after all identifiable bleeding points have been ligated. Great care is taken to avoid any dead space in the depth of the wound. Drains are introduced alongside the wound closure. If the depth of the wound cannot be completely closed with mattress sutures, then drains are introduced into the wound and the sutures are tied over these drains.

C, Through-and-through-wounds of the liver parenchyma, usually caused by missiles, are treated by the introduction of suction catheters through the wound of exit and the wound of entrance. Suction is applied on the operating table and if the oozing of blood and bile from the wounds stops and the aspiration of blood and bile through the catheters is negligible, then no further operative treatment is instituted. Suction is continued in the postoperative phase until all secretions have stopped and the catheters are then slowly removed.

D and *E*, In *deep central fractures* from blunt trauma, part of a lobe is often incompletely amputated. This amputation is surgically completed by severing the small bridge of liver tissue connecting the damaged liver to the healthy body of liver. In this illustration the finger fracture technique of the hepatic tissue to be removed is demonstrated. All of the devitalized tissue is thus removed. Vessels and bile ducts are carefully sutured. Since the suturing, especially of bile ducts, can never be entirely complete the raw surface of the liver is carefully drained. Two of three such drains used routinely are shown in this illustration. The third drain is introduced along the anterior border of the liver resection.

clean, sharp lacerations of the common or hepatic bile ducts, primary reconstruction with 5–0 Dexon and without intraluminal stent is the method of choice.

The area of repair is drained. If there is loss of tissue, such as in gunshot wounds, the irregular ends of the duct(s) should be refreshened and a primary anastomosis over a stent attempted. An intraluminal stent is employed in these cases since the anastomotic edges are most precarious and since more fibrous circumferential scarring will occur. Sufficient duct length for tension-free anastomosis can always be obtained by liberating the distal duct and the duodenum through a Kocher maneuver.

Primary choledocho-Roux-en-Y jejunostomy is only indicated in lacerations caused by blunt injury where much damage has been inflicted to the duodenum and pancreas and where pancreatoduodenectomy represents the safest method of debridement and hemostasis. It is also preferred in those patients in whom the need for operation was not recognized at the time of the original blunt injury and a delayed operation uncovers much tissue loss.[49]

It has been stated that blood supply to and biliary drainage from at least one lobe of the liver is mandatory for survival. This implies that the lobe which is not supplied with vessels and bile duct must and can be resected, if a serious attempt at repair is not successful.

Excisional Techniques

In *deep central fractures* from blunt trauma part of a lobe is often incompletely amputated, with only a small bridge of liver tissue connecting the irreparably damaged tissue to the healthy body of liver. In such cases, the accidental amputation is completed by finger fracture of the connecting bridge. Since all such liver wounds have fjord-like extensions into the remaining body of liver parenchyma, all the questionably viable tissue is removed. Careful hemostasis is performed by suture ligatures or hemoclips (Fig. 3 *D* and *E*).

In *extensive stellate central fractures,* all or most of one lobe may be involved. In order to fully satisfy all the principles of wound debridement and hemostasis, a formal anatomic lobectomy represents the most expedient and safest solution to this formidable problem.[2, 4, 10, 12, 13, 21, 27, 29, 33, 47] (Figs. 4 and 5). For a right lobectomy, the incision should be extended into the seventh or eighth intercostal space or preferably upward via median sternotomy.

The right lobe is composed of an anterior and posterior segment, the left lobe has a medial and lateral segment. The division between the right and left lobes follows a plane extending from the fossa of the gallbladder anteriorly to the inferior vena cava posteriorly. On the right side stellate lacerations may extend beyond the anatomic confines of the right lobe and an extended right lobectomy is then indicated, taking with the resected specimen part of the medial segment of the left lobe. On the left side stellate lacerations are often confined to the lateral segment.[26] Intimate knowledge of hepatic anatomy is a prerequisite to successful hepatic lobectomy and for this the reader is referred to the ana-

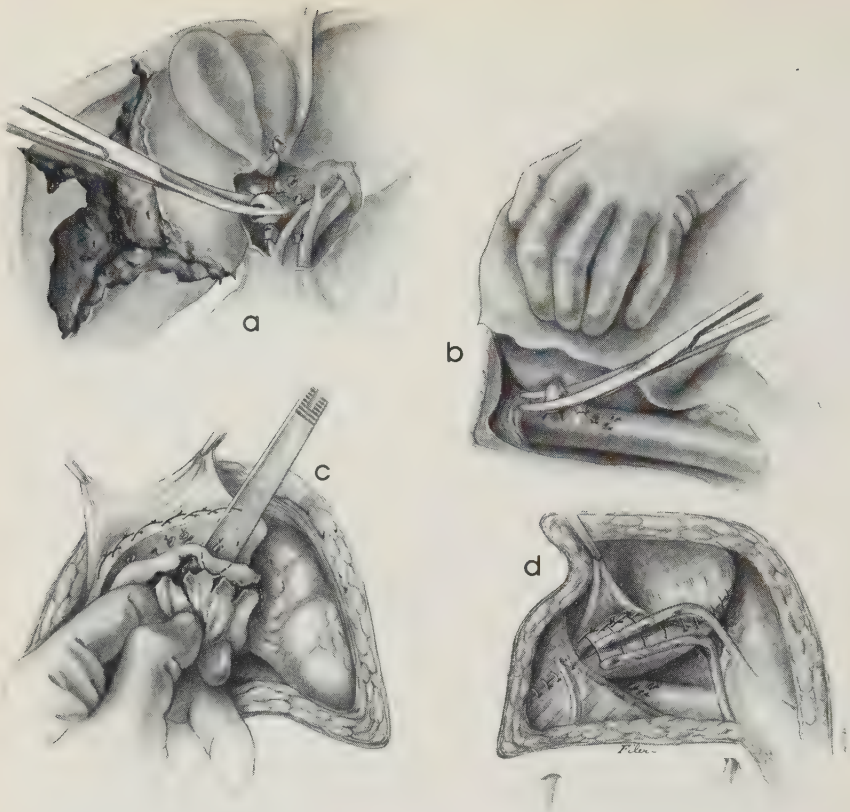

Figure 4. Right hepatic lobectomy and extended lobectomy. *A*, After identifying the structures of the porta hepatis, the cystic duct, the right hepatic duct and the right hepatic artery have been severed between ligatures. The right branch of the portal vein is being transsected between two ligatures. In an extended right lobectomy the middle hepatic artery would also be severed between ligatures if it does come off the left hepatic artery, as is the case in this illustration.

B, After all the right-sided structures of the porta hepatis have been controlled, the right lobe of the liver is rotated anteriorly and to the left. The retrohepatic portion of the inferior vena cava is then approached and liberated. The small veins entering from the right lobe are severed between ligatures. The large most superior right hepatic vein is identified from the middle and left veins and is then transsected between ties. In an extended right lobectomy, the middle hepatic vein is also included in this dissection.

C, The right lobe is now removed. For a simple right lobectomy the division of liver parenchyma runs along a plane extending from the fossa of the gallbladder anteriorly to the inferior vena cava posteriorly.

For an extended right lobectomy the line of transsection of the liver tissue runs in the plane of the left sagittal fissure parallel to the falciform ligament as is illustrated in this drawing. Prior to incising the liver capsule a row of interlocking sutures is helpful in avoiding blood loss. However, this row of sutures is not a must since it does somewhat increase liver necrosis at the cut edge.

Dissection of liver tissue by the blunt end of a knife handle is demonstrated here.[10, 13, 35] The vascular structures and bile ducts resist the gentle pressure of the dissecting knife handle and are suture ligated.

D, In a simple right lobectomy the raw surface of the liver is left open, after careful hemostasis, closure of bile ducts and drainage, as illustrated in Figure 3*E*.

In extended right hepatic lobectomy the only remaining tissue is represented by the lateral segment of the left lobe. The anteroposterior diameter is small at this level and hence it is possible to approximate the anterior and posterior margins of the cut surface and to bring the falciform ligament over this suture line.[13] If the closure of the raw surface is possible without too much tension—so as to avoid necrosis of the liver edges—then two drains are used alongside the closed resection area as illustrated here. A chest drain is also required if a right lateral extension of the primary midline incision was used.

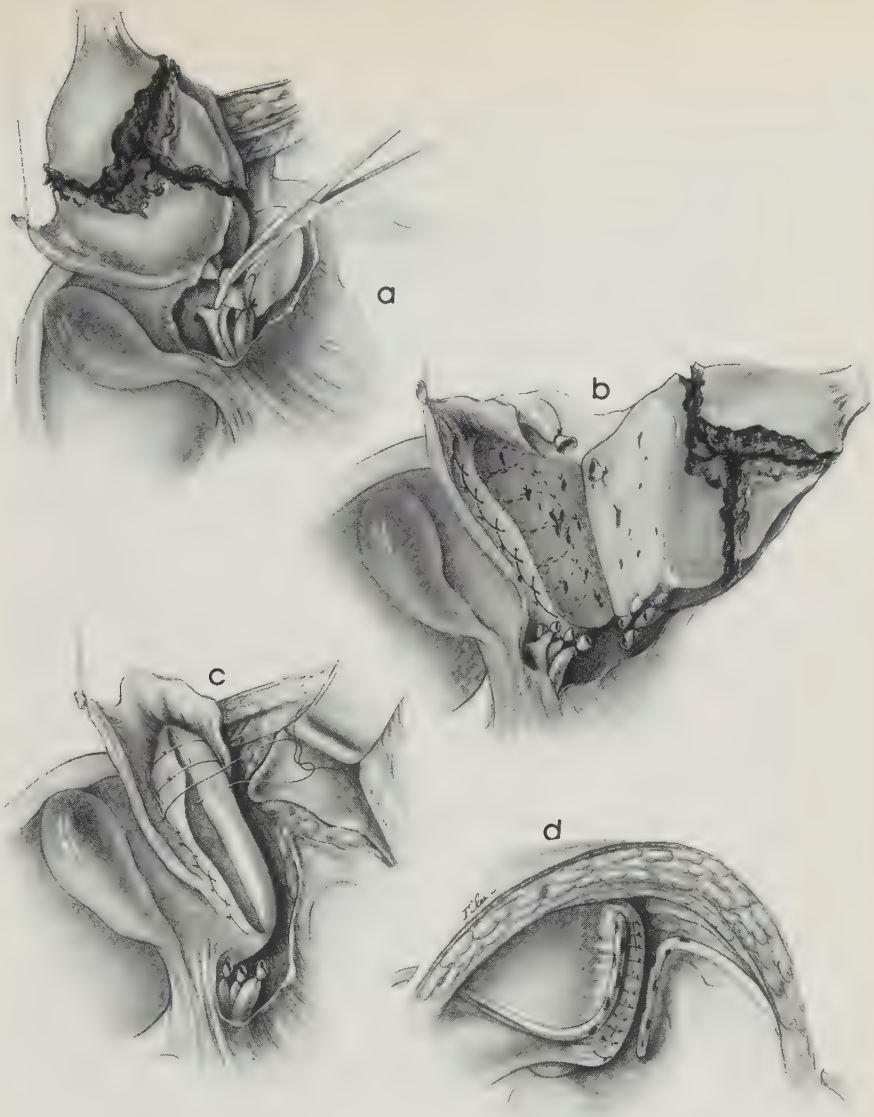

Figure 5. Lateral segmentectomy, left lobe. *A*, In order to mobilize the lateral segment of the left lobe and allow for an easier approach to the structures of the porta hepatis, the ligamentum teres has been severed between ties and the left lateral and left coronary ligaments have been divided. The structures of the left side of the porta hepatis are identified. The left branch of the portal vein, often the easiest structure to handle first from a left-sided approach, is severed between two ligatures.

B, The left hepatic artery and duct are identified next and are transsected between ligatures. The middle hepatic artery arising either from the left or right branch of the common hepatic artery is carefully respected, since it supplies blood to the middle segment of the left lobe.

The liver is relatively thin at the line of proposed transsection and hence control of bleeding with interlocking sutures is easily obtained. However, such sutures, if they are too tight, do produce necrosis and individual suture ligation of all vessels and bile ducts may be preferable. Both techniques are demonstrated in this drawing.

At the apex of the line of transsection the left hepatic vein is dissected with great care, so as not to injure the right or middle hepatic veins. After positive identification of the left hepatic vein it is severed between ligatures.

C, The management of the raw surface of the liver is a matter of personal preference. The approach such as it is shown in Figure 3*E* may be used. On the other hand since the liver is relatively thin at this level, the raw surface may be closed by approximating its anterior and posterior margins and by pulling the falciform ligament over this closure.[13] *D*, If the line of liver resection has been closed primarily only two drains are placed – one posterior and one anterior to the cut surface.

tomic studies of Healey,[16] Goldsmith and Woodburne,[15] and Donovan, Turrill, and Facey.[11] Consultation of an up-to-date anatomic atlas in the operating room, in the unexpected event of hepatic lobectomy, is not a sign of mental weakness but proof of superior wisdom.

The individual steps in hepatic lobectomy are illustrated in Figures 4 and 5 and are described in the corresponding legends. This description is not repeated in this text, since the number of pages devoted to such a description together with the necessary volume of illustrative material seems to confer a special importance to hepatic lobectomy and often conveys to the casual or younger reader the impression that anatomic lobectomy should be applied somewhat indiscriminately to most or all serious lacerations of the liver. Nothing could be farther from reality.[18, 25, 27, 29, 32] Planned anatomic lobectomy has its clear indications limited essentially to complete destruction of a lobe; but by far, the vast majority of liver injuries can be safely managed by one of the lesser techniques shown in Figure 3.

Recently, Tien-Yu Lin[50] has presented a new method for rapid major liver resections. In this technique he uses specially designed clamps, after the ligaments of the affected lobe have been divided and the liver has been freed from the diaphragm. A soft-bladed clamp with metal teeth on one blade gently compresses the healthy liver parenchyma to prevent leakage of bile and blood, while a sturdily-built crush clamp is used to transect the liver parenchyma at the elected site of resection. Prior to application of the crush clamp the liver capsule is incised at the site selected for the parenchymal crush. The cystic duct and artery are also divided in right lobectomies. However, the hepatic artery, portal vein, hepatic duct and hepatic vein(s) involved in the resection are ligated and severed only after the crush has been performed. On release of the crush clamp, the vascular and ductal structures stand out as whitish cords in the depth of the resection site. In 5 hepatic resections done for primary liver cell carcinoma, Lin used an average of 200 ml of blood in each case and his operation time averaged 1.5 hours. While at first glance this technique seems to be rather coarse, it probably does not create any more liver necrosis than the tedious parenchymal finger fracture method. It has the advantage of minimal transfusion needs, speed, apparent safety, and great ease of application, and may well become the technique of choice in major hepatic resections for trauma, especially in the hands of the occasional liver surgeon.

Special Situations

In a *subcapsular hematoma* it is difficult to evaluate the extent of the underlying parenchymal damage without opening the hematoma.[24] If the hematoma is left intact, postoperative rupture of the capsule and secondary hemorrhage may occur. Therefore, all such hematomata should be opened, the extent of the underlying damage evaluated, and the surgical technique best suited to manage a given lesion used.[5, 47] This opinion is not shared by all authors. Richie and Fonkelsrud have followed 4 patients with subcapsular hematomas and the reabsorption of the hematomas was documented by serial scans. These patients were stable and did not require operation.[36]

Deep "bursting" lacerations of the liver with an intact and normal appearing hepatic crust are very difficult to diagnose intraoperatively. Very often the increased volume of a lobe and the tenseness of the capsule will lead the suspicious surgeon to an exploratory needle aspiration of blood and bile followed by an x-ray contrast study through the same needle. If a central cavity is thus confirmed, it should be entered and the damage evaluated under direct vision. Most often a partial lobectomy or a formal lobectomy is indicated. Great help can be obtained intraoperatively from *cholangiography and angiography*,[2, 11] both in the diagnosis of occult lesions and in the control of surgical reconstruction. Ideally, both techniques should be available. Cholangiography alone may be an acceptable compromise, and no hospital should be without it for emergency as well as elective hepato-biliary operations.

Control of Threatening Exsanguination

Major hemorrhage may occur from lacerations of the hepatic artery(ies) and portal vein; deep stellate liver lacerations; wounds of the inferior vena cava and wounds or avulsions of the hepatic veins. In patients with such serious lesions the surgeon is often greeted by blood—both liquid and clotted—upon opening the abdomen. As he strives to gain control of the situation an announcement is made from the head of the table that the patient's vital signs are deteriorating. Under these circumstances all intra-abdominal manipulations should be abandoned temporarily and the abdominal aorta compressed against the spine directly below the diaphragm by the surgeon's fist or a sponge stick. The patient is put in moderate Trendelenburg position, volume is replaced at an accelerated rate and the surgical assistant removes clotted blood and aspirates liquid blood and bowel contents, taking care not to displace intraabdominal organs. As the patient's condition improves, a more thorough peritoneal toilet and examination of the injuries at hand can be undertaken.

Based on the findings, plans are made to proceed with the operation through the present incision or to enlarge it, to call for vascular instruments and sutures, to prepare an intravascular bypass tube, and to accelerate hypothermia by placing ice-filled plastic bags against the extremities and the head and neck. Depending upon the level of improvement, the surgeon may continue to compress the aorta or to release it slowly, while the blood pressure and pulse are monitored continuously. The total time of compression should not exceed 15 minutes. Aortic compression may be resumed after a few minutes of distal perfusion if the abdominal bleeding is not under complete control.

Finger compression of the hepatoduodenal ligament as described by Pringle[34] is indicated in the evaluation and initial management of bleeding from the hepatic vessels and from the depth of a central liver fracture. In most liver lacerations, even the very extensive ones, active bleeding has usually stopped and a slow ooze persists once all clots and accumulated liquid blood have been evacuated. Continued hilar compression is therefore rarely necessary during the entire duration of operative control of bleeding from parenchymal lacerations. However, if

dark blood continues to well up from the depth of a liver wound, after successful compression of the hepatoduodenal ligament, an inferior vena cava or hepatic vein laceration should be strongly suspected.[20, 29, 47] If the blood is bright, significant collateral arterial circulation is the more likely cause. Finger compression should be replaced by an atraumatic clamp in order to free both hands. Rubber-shod clamps are usually too bulky in this area and have a tendency to slip, and linen shod or vascular clamps are preferred. For parenchymal laceration an expeditious hilar dissection is then indicated, the blood supply to the involved lobe is occluded, the linen-shod clamp is removed and perfusion of the healthy liver is thus resumed. In injuries to the hepatic artery(ies) and/or portal vein the linen-shod clamp is replaced by vascular clamps as soon as both ends of the vessel have been liberated.

For the management of inferior vena cava and hepatic vein injuries the placement of an internal shunt as recommended by Schrock and associates gives the best chance of success.[39] This shunt may be placed from below through the opened suprarenal portion of the inferior vena cava[9, 24] or from above through the right atrial appendage.[39] Positioning of this shunt will require occlusion of the vena cava around the shunt by umbilical tapes both below and above the liver. Superiorly, this is best achieved by isolating the inferior vena cava within the pericardium, following a lateral or mediastinal extension of the original midline incision. Temporary occlusion of the liver hilus by a bulldog clamp is also required in order to interrupt all blood flow to and from the hepatic veins.[34] Mays has described a nice catheter in which a long cylindrical balloon isolates the entire retrohepatic inferior vena cava, obviating the need for encircling tapes.[25, 26] (Fig. 6). Since all this is more easily said than done, freedom of action for the positioning of the shunt may be achieved by compressing the aorta temporarily below the diaphragm, occluding the inferior vena cava below and above the liver and compressing the porta hepatis with a soft or vascular clamp.[12, 17]

Other maneuvers such as complete occlusion of the suprarenal inferior vena cava only,[29] "quick" exposure of the retrohepatic inferior vena cava or of the inferior vena cava-hepatic vein junction, and precise applications of vascular clamps in a field of clots and fresh blood are usually doomed to failure. Once the site of bleeding has been exposed, if a hepatic vein is involved, repair or ligation should be expeditious to permit relief of the hepatic hilar compression as soon as possible.

Drainage

All hepatic wounds should be drained, even superficial ones that are completely dry at the time of exploration.[24] For superficial wounds soft Penrose drains are best. Straight or sump aspiration drains are used in all other situations in order to evacuate blood and bile as fast and as completely as possible. Since drains are easily displaced inside the body once the abdomen is closed, they should be anchored in the desired position with sutures of 5–0 catgut taken in minimal bites of fat, peritoneum, liver capsule, or diaphragm. After partial or complete lobectomy a minimum of three drains is used: one posteriorly; one along the

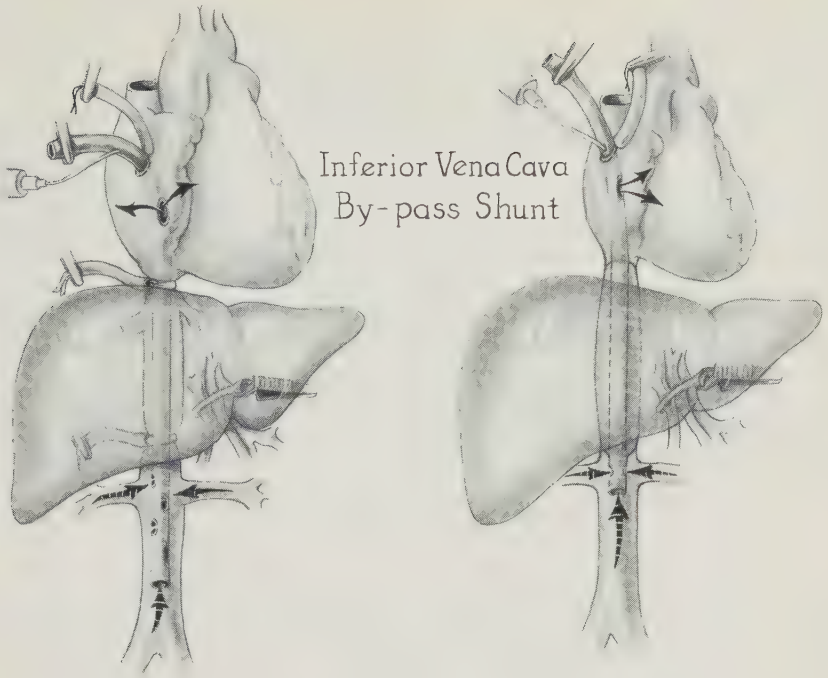

Figure 6. Inferior vena cava bypass shunt as proposed by Schrock[39] and Mays.[25, 26] The shunt is placed through the right atrial appendage and is passed beyond the level of the renal veins. Tapes are placed around the vena cava above and below the liver, allowing flow from the distal vena cava and the renal veins into the atrium. Side holes located in the atrium allow for blood flow from the tube. In order to interrupt flow from the hepatic veins, the hilar vessels are occluded temporarily. The atrial end of the bypass, brought out through the atriotomy, may be clamped or may be used for the infusion of fluids and blood.

If time does not allow for a mediastinotomy, the inferior vena cava bypass shunt may be introduced through an incision in the infrahepatic portion of the inferior vena cava. In this case the superior end of the tube is gently pushed into the atrium and comes to rest there after some resistance has been encountered to further progression of the tube. The lower end of the tube has to be pushed downwards through the vena cava incision to the level of the renal veins. In this approach the inferior vena cava is snared around the bypass shunt below the phlebotomy used for introduction of the tube. A circumferential snare of the vena cava above the liver is also necessary. Pringle's maneuver is used to interrupt hepatic venous flow. Mays has proposed the usage of a catheter introduced through the atrial appendage. A long cylindrical balloon that comes to rest in the retrohepatic portion of the inferior vena cava isolates this entire area when it is inflated. This obviates the need for encircling tapes. (By permission of Contemporary Surgery, McGraw-Hill, New York.)

raw liver surface; one anteriorly. Since most patients will hopefully sit up and ultimately walk after operation, it should be realized that what seems to be the most dependent exit through the abdominal wall with the patient on the operating table is not necessarily the most dependent position with the patient standing or sitting. In view of the very questionable benefits obtained from and the possible harm done by intraluminal drainage of an intact common duct, we do not subscribe to T-tube drainage as advocated by Merendino.[22, 23, 30]

Postoperatively, the management of drains depends on the condition for which they are used. Penrose drains are twisted as soon as all drainage has stopped and are then removed progressively over a period

of 2 days if drainage does not recur and the patient is afebrile. If there was never drainage, the total period of twisting and removal extends from 3 to 5 days postoperatively. Drains introduced into the liver or along its raw surface after lobectomy are left in place until all drainage has stopped or has diminished to a trickle. The drain is then twisted and if no further drainage occurs and the patient remains afebrile, the drain is anchored above skin level with a safety pin and removed progressively over a 2-day period. Drains that are dry should be removed within 48 hours since they act as a wick for the entry of bacteria. If a drain continues to produce appreciable amounts of bile over a prolonged period of time or if the patient continues to be febrile and pus is aspirated, then a study with contrast material through the tube is indicated as soon as the drainage tract has matured (usually after 10 days). A parenchymal biliary fistula or an incompletely drained cavity requiring reoperation may thus be identified.

POSTOPERATIVE CARE

Broad-spectrum *antibiotics* started preoperatively or intraoperatively should be continued in the postoperative period.[4, 11] All drainage is cultured and if organisms are grown, prolonged antibiotic coverage is based on the sensitivity studies obtained.

Metabolic deficiencies that are particular to large hepatic resections have been described by McDermott.[2, 28] They include hypoglycemia particularly in the first 48 hours, hypoalbuminemia, and bleeding diathesis. Hypoglycemia should be treated with infusions containing 10 per cent glucose, in the first 72 hours.[4] Hypoalbuminemia is best treated by concentrated salt-poor albumin. Bleeding may be due to decreasing levels of prothrombin or fibrinogen; more often it is due to the administration of large quantities of stored blood. Vitamin K and fibrinogen should be administered if they are found to be deficient. Thrombocytopenia is treated by the administration of platelet concentrates or of very fresh whole blood. More complicated coagulopathies such as low levels of factor VII and intravascular coagulation are best handled in consultation with a hematologist.

Careful debridement, compulsive hemostasis, meticulous suturing of injured ducts, proper drainage of hepatic wounds, and religious avoidance of tamponade by packs should lead to a smooth postoperative course, free of lingering or overt *infections, secondary hemorrhage, biliary fistulas and hemobilia.* Alas, reality is far from this ideal situation, even for the most careful surgeons. Intrahepatic or perihepatic infection, once recognized, is localized by needle aspiration, contrast injections of sinus tracts, and possibly arteriography. The problem is essentially one of subphrenic sepsis and should be handled by drainage and adequate antibiotics.[19]

Secondary hemorrhage after the first postoperative week is due to sepsis and necrosis of devitalized liver tissue. Unless it is massive and persistent, nonoperative therapy and blood transfusions are indicated. Ar-

teriography may be helpful in localizing massive bleeding. Reoperation is most difficult. Three approaches are possible: Dissection and ligation of the bleeding point in healthy tissue; temporary occlusion of the corresponding artery and, if successful, ligation of the artery; further hepatic parenchymal resection.

Biliary fistulas should be studied by contrast injections and if a persistent cavity is responsible it should be drained. If this is not the case, biliocutaneous fistulas should be treated by prolonged observation. Rarely is a secondary hepatic resection indicated.

Hemobilia, a complication recognized with greater frequency in recent times, is discussed in the article on Liver Injuries in Children.[38, 41, 45]

Other complications such as pulmonary sepsis, "shock or wet" lung syndrome, stress ulcerations of the upper gastrointestinal tract, intestinal obstruction, phlebothrombosis, pulmonary embolism, and renal failure are encountered with increased frequency in severe liver trauma as they are in other major traumatic conditions.

SUMMARY

A successful approach to the treatment of hepatic trauma includes careful clinical evaluation of the injured patient and aggressive management of shock with early transfer to the operating room. The principles involved in the treatment of a liver injury are those used in the surgical management of any major wound: debridement, hemostasis, and drainage. Difficult wounds of the liver parenchyma and hilus may be approached by temporary compression of the abdominal aorta or of the structures in the hepatoduodenal ligament. Injuries of the inferior vena cava and of the hepatic veins are best handled by a complex approach consisting in the extension of the incision laterally or superiorly and the introduction of a bypass shunt into the inferior vena cava. At times segmentectomy or lobectomy represents the fastest and safest means of debridement. Early recognition of the need for operation and proper application of all the principles of wound management will reduce mortality and postoperative morbidity such as infection, secondary hemorrhage, biliary fistula, and hemobilia.

REFERENCES

1. Aakhus, T., and Enge, I.: Angiography in rupture of the liver. Acta Radiol., *11*:353, 1971.
2. Ackroyd, F. W., Pollard, J., and McDermott, W. V.: Massive hepatic resection in the treatment of severe liver trauma. Amer. J. Surg.,*17*:442, 1969.
3. Amerson, J. R., and Stone, H. H.: Experiences in the management of hepatic trauma. Arch. Surg., *100*:150, 1970.
4. Aronsen, K. F., Bengmark, S., Dahlgren, S., et al.: Liver resection in the treatment of blunt injuries to the liver. Surgery, *63*:236, 1968.
5. Balasegaram, M.: Blunt injuries to the liver. Ann. Surg., *169*:544, 1969.

6. Bernhard, W. F., McMurray, J. D., and Curtis, G. W.: Feasibility of partial hepatic resection under hypothermia. New Eng. J. Med., *253*:1959, 1955.
7. Block, G. E.: *In* Discussion of the Management of Liver Trauma by Owens, M. P., Wolfman, E. F., Chung, G. K.: Arch. Surg., *103*:215, 1971.
8. Boijsen, E., Judkins, M. P., and Simay, A.: Angiographic diagnosis of hepatic rupture. Radiology, *86*:66, 1966.
9. Buckberg, G. D., Ono, H., Joseph, W. L., et al.: Hypotension following revascularization of the anoxic liver. Surgery, *63*:446, 1968.
10. Byrd, W. M., and McAfee, D. K.: Emergency hepatic lobectomy in massive injury to the liver. Surg. Gynec. Obstet., *113*:103, 1961.
11. Donovan, A. J., Turrill, F. L., and Facey, F. L.: Hepatic trauma. SURG. CLIN. N. AMER., *48*:1313, 1968.
12. Donovan, A. J., Michaelian, M. J., and Yellin, A. E.: Anatomical hepatic lobectomy in trauma to the liver. Surgery, *73*:833, 1973.
13. Foster, J. H., Lawler, M. F., Welborn, M. B., Jr., et al.: Recent experience with major hepatic resection. Ann. Surg., *167*:651, 1968.
14. Freeark, R. J., Shoemaker, W. C., and Baker, R. J.: Aortography in blunt abdominal trauma. Arch. Surg., *96*:705, 1968.
15. Goldsmith, N. A., and Woodburne, R. T.: The surgical anatomy pertaining to liver laceration. Surg. Gynec. Obstet., *105*:310, 1957.
16. Healey, J. E., Jr.: Clinical anatomic aspects of radical hepatic surgery. J. Int. Coll. Surg., *22*:542, 1954.
17. Heaney, J. P., Stanton, W. K., Halbert, D. S., et al.: An improved technique for vascular isolation of the liver: Experimental study and case reports. Ann. Surg., *163*:237, 1966.
18. Jordan, G. L., and Beall, A. C., Jr.: Diagnosis and management of abdominal trauma. Current Prob. Surg., November 1971.
19. Konvolinka, C. W., and Olearczyk, A.: Subphrenic abscess. Current Prob. Surg., January 1972.
20. Lim, R. C., Jr., Knudson, J., and Steele, M.: Liver trauma. Arch. Surg., *104*:544, 1972.
21. Lortat-Jacob, J. L., and Robert, H. G.: Hépatectomie droite règlée. Presse Méd., *60*:549, 1952.
22. Lucas, C. E., and Walt, A. J.: Critical decisions in liver trauma. Arch. Surg., *101*:277, 1970.
23. Lucas, C. E.: Prospective clinical evaluation of biliary drainage in hepatic trauma: An interim report. Ann. Surg., *174*:830, 1971.
24. Madding, G. F., and Kennedy, P. A.: Trauma to the Liver. Philadelphia, W. B. Saunders Co., 1971.
25. Mays, E. T.: Complex penetrating hepatic wounds. Ann. Surg., *173*:421, 1971.
26. Mays, E. T.: Lobectomy, sublobar resection and resectional debridement for severe liver injuries. J. Trauma, *12*:309, 1972.
27. McClelland, R. N., and Shires, G. T.: Management of liver trauma in 259 consecutive patients. Ann. Surg., *161*:248, 1965.
28. McDermott, W. V., Jr., Greenberger, N. J., Isselbacher, K. J., et al.: Major hepatic resection: Diagnostic techniques and metabolic problems. Surgery, *54*:56, 1963.
29. Mercadier, M. P., Clot, J. P., and Cady, J. P.: Right hepatectomy in the treatment of liver trauma. Amer. J. Surg., *124*:353, 1972.
30. Merendino, K. A., Dillard, D. H., and Cammock, E. E.: The concept of surgical biliary decompression in the management of liver trauma. Surg. Gynec. Obstet., *117*:285, 1963.
31. Miller, D. R.: Median sternotomy extension of abdominal incision for hepatic lobectomy. Ann. Surg., *175*:193, 1972.
32. Morton, J. R., Roys, G. D., and Bricker, D. L.: The treatment of liver injuries. Surg. Gynec. Obstet., *134*:298, 1972.
33. Pearlman, D. M., and Grayer, S.: Emergency right hepatic lobectomy for rupture due to blunt injury. Amer. J. Surg., *117*:421, 1969.
34. Pringle, J. H.: Notes on the arrest of hepatic hemorrhage due to trauma. Ann. Surg., *48*:541, 1908.
35. Quattelbaum, J. K., and Quattelbaum, J. K., Jr.: Technique of hepatic lobectomy. Ann. Surg., *149*:648, 1959.
36. Richie, J. P., and Fonkelsrud, E. W.: Subcapsular hematoma of the liver. Arch. Surg., *104*:781, 1972.
37. Root, H. D., Houser, C. W., McKinley, C. R., et al.: Diagnostic peritoneal lavage. Surgery, *57*:633, 1965.
38. Sandblom, P.: Hemobila (Biliary Tract Hemorrhage). Charles C Thomas, Springfield, Illinois, 1972.
39. Schrock, T., Blaisdell, F. W., and Mathewson, C., Jr.: Management of blunt trauma to the liver and hepatic veins. Arch. Surg., *96*:698, 1968.

40. Shaftan, G. W.: Indications for operation in abdominal trauma. Amer. J. Surg., *99*:657, 1960.
41. Steichen, F. M., and Sheiner, N. M.: Traumatic intrahepatic hemobilia. Arch. Surg., *92*:838, 1966.
42. Steichen, F. M.: Penetrating wounds of the chest and the abdomen. Current Prob. Surg., August 1967.
43. Steichen, F. M., Efron, G., Pearlman, D. M., et al.: Radiographic diagnosis versus selective management in penetrating wounds of the abdomen. Ann. Surg., *170*:978, 1969.
44. Steichen, F. M.: The emergency management of the severely injured. J. Trauma, *12*:786, 1972.
45. Steichen, F. M.: Management of intrahepatic hemobilia by hepatic resection. Contemp. Surg., *3*:71, 1973.
46. Stephens, G. L., and Amis, R. E.: Polyethylene tube technique of diagnostic paracentesis. J. Trauma, *5*:805, 1963.
47. Trunkey, D. D., Shires, T., and McClelland, R.: Management of liver trauma in 811 consecutive patients. Ann. Surg., *179*:722, 1974.
48. Thal, E. R., and Shires, G. T.: Peritoneal lavage in blunt abdominal trauma. Amer. J. Surg., *125*:64, 1973.
49. Zollinger, R. M., Jr., Keller, R. T., and Hubay, C. A.: Traumatic rupture of the right and left hepatic ducts. J. Trauma, *12*:563, 1972.
50. Tien-Yu Lin: A simplified technique for hepatic resection; the crush method. Ann. Surg., *180*:285, 1974.

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Postoperative Jaundice

Mechanism, Diagnosis and Treatment

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Although not an infrequent occurrence, postoperative jaundice is a complex diagnostic and therapeutic clinical problem.[31] While all major surgical procedures can be followed by postoperative jaundice, surgical procedures within the upper abdomen, usually for suspected biliary tract or peptic ulcer disease, are more frequently complicated by such an untoward event. Such increased frequency is due primarily to the anatomic vulnerability of the extrahepatic biliary structures during these procedures.

As might be expected, postoperative jaundice is usually the consequence of multiple factors working in concert. Among the many factors that need to be evaluated in any given situation are: (1) the patient's preoperative liver function, (2) any history of prior alcohol abuse, drug exposure, or infectious agent exposure, (3) the reason for the original surgical procedure, (4) the type and duration of the procedure, (5) the type of anesthetic used, (6) the intraoperative findings, (7) the number of units and age of transfused blood given before, during and after the procedure, (8) any history of shock, hypoxia, or infection before, during or after the surgical procedure, (9) any history of preexisting medical condition, such as congestive heart failure, anemia, hemolytic disease, or bleeding diathesis, that might predispose the individual to develop jaundice.

Because several of these etiologic factors usually obtain in a given case of postoperative jaundice, considerable clinical acumen is required to identify those cases in which an additional, usually difficult, high-risk operation is required from those in which continued medical management is indicated. When faced with such a difficult diagnostic challenge, it is advantageous to consider each of the possible contributing factors as it relates to the three basic mechanisms responsible for jaundice.[38] These three mechanisms are: (1) prehepatic defect—an increased

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pigment load, (2) intrahepatic defect—impaired bilirubin conjugation and/or excretion due to some abnormality of hepatocellular function, and (3) posthepatic defect—an inability to excrete conjugated bilirubin. The advantage of such an approach is that only those situations listed under the latter, e.g., posthepatic defects will require additional operation.

PREHEPATIC DEFECTS—INCREASED PIGMENT LOAD

The potential sources of an increased pigment load in the postoperative state are (a) hemolysis of transfused blood (old or mismatched), (b) the mild nonspecific hemolysis which occurs after major injury,[8, 44] and, (c) reabsorption of extravasated blood. Although massive spontaneous hemolysis of the patient's own erythrocytes is a rare occurrence, it must be considered in those patients with a family or personal history of intrinsic erythrocyte defects (such as sickle cell anemia, thalassemia, glucose 6-phosphate dehydrogenase deficiency and others) as well as in those patients with histories of autoimmune or neoplastic conditions that are often associated with Coombs-positive hemolytic anemias.[26] The hospital record should be reviewed for the numerous drugs that are known to induce hemolysis (Table 1). The hemolysis in all such cases results in moderate biochemical and mild clinical jaundice of the unconjugated variety (e.g., no more than 15 per cent conjugated bilirubin,

Table 1. *Drugs That Can Produce Jaundice*

Drugs that have been reported to induce hemolysis in patients with intrinsic red cell defects

Acetaminophen	Furazolidone	Procainamide
Acetanilid	Menadione	Pyribenzamine
Acetylsalicylic acid	Mepacrine	Pyrimethamine
p-Aminophenol	Methylene Blue	Quinidine
p-Aminobenzoic acid	Naphthalene	Quinine
Aniline	Neoarsphenamine	Sulfasoxazole
Antistine	Nitrofuradantin	Sulphamerazine
Ascorbic acid	Nitrofurazone	Sulphathiozole
Chloramphenicol	Pamaquin	Sulphamethoxypyridine
Chloroquine	Pentaquin	Sulphanilamide
Dapsone	Phenacetin	Sulphaseazine
Cimercapol (BAL)	Phenylhydrazine	Toluidine Blue
Diphenhydramine	Primaquine	
Furaltodone	Probenamid	

Drugs that can provoke an immune-hemolysis

Amidopyrine	Insecticides	Quinine
Antazoline	Insulin	Rifampicin
p-Aminosalicylic acid	Isonicotinic acid hydrazide	Stibophen
Cephalosporins	Penicillin	Sulfonamides
Chlorpromazine	Phenacetin	Sulfonylureas
Dipyrone	Quinidine	

rarely greater than 3.5 mg per 100 ml, unless some other coexistent hepatic disease is also present).[1] In addition, the hepatic transaminases and alkaline phosphatase activities are normal while the haptoglobin is greatly reduced or absent, a reticulocytosis is present, as well as hemosiderinuria. The major problem in these situations is diagnosis. Once recognized, therapy is relatively simple. First, the circulation has to be maintained with adequate replacement of fluids and blood and second, if hemolysis is severe, the urine output must be maintained with appropriate intravenous fluids, alkalinization, and diuresis in order to prevent renal failure because of the hemoglobinemia and resultant hemoglobinuria.[46] Other usually less dramatic causes of hemolysis include the normal destruction of transfused red cells and infection. The observation that 10 to 15 per cent of transfused blood which is 2 weeks or more old hemolyzes within 24 hours explains the increased pigment load and resultant jaundice in those patients requiring massive transfusion.[29] The size of such an increased load can easily be appreciated when one considers that a single unit of whole blood with a hemoglobin content of 15 gm per 100 ml contains a total of 75 gm of hemoglobin which yields about 250 mg of bilirubin when 10 per cent undergoes hemolysis. It is this additional 250 mg of bilirubin per unit of transfused blood, which needs to be excreted by the liver in addition to the daily normal bilirubin load, which can overload the liver's excretory mechanisms. Similarly, large hematomas or pools of extravasated blood (hemoperitoneum, hemothorax, etc.) can provide significant additional bilirubin loads for hepatic excretion as they are absorbed.

Infection, especially sepsis, with any of a large number of different bacteria including streptococci, E. coli, Bacteroides and Clostridia can also result in hemolysis.[9, 20] The mechanisms responsible are poorly understood but presumably hemolysis is due to bacterial hemolysins, and reduced hepatic uptake of bilirubin also occurs due to the concurrent hypotension and reduced hepatic perfusion.

Finally, another pigment which can discolor plasma as well as urine is myoglobin. Myoglobinemia can be seen following large soft tissue injuries which are common in trauma victims or burn patients.[37] Myoglobin, which is a smaller molecule than hemoglobin and which is not bound to haptoglobin, and is thus more filterable, appears in urine even when formed in small amounts. Thus, these patients must be managed like those with massive intravascular hemolysis and jaundice, with fluids, alkalinization, and diuresis in order to prevent acute renal shutdown.

AN INTRAHEPATIC DEFECT—IMPAIRED BILIRUBIN EXCRETION DUE TO HEPATOCELLULAR INJURY

The great bulk of cases of postoperative jaundice are a result of intrahepatic abnormalities (i.e., hepatocellular injury). In terms of frequency, the two most common and usually coexistent causes of postoperative jaundice due to hepatocellular injury are hypotension[32] and

hypoxia.[42] Either or both of these two conditions may have been present before, during, and/or after operation and become manifestly important as jaundice is noted postoperatively. The pathophysiologic mechanisms responsible for the hepatocellular damage in situations of shock and inadequate ventilation or perfusion states is easily appreciated when one realizes that 70 per cent to 80 per cent of the total hepatic blood flow and probably 70 per cent of the liver's oxygen supply is made up of portal venous blood.[24] Normally, hepatic venous oxygen saturation is 35 to 50 per cent; in shock this can be reduced to as low as 6 per cent as visceral perfusion is reduced. The use of vasopressors in shock causes an additional decrease in total hepatic blood flow and thereby increases hepatic hypoxia by further shunting blood away from the viscera.[6] Since the centrolobular cells are bathed in blood with the lowest oxygen content, the hepatocellular necrosis seen in liver biopsies obtained from patients during states of low flow or hypoxia is manifested by focal hepatocellular drop-out and pigment phagocytosis about the central veins.[30, 35] Considering the frequency of this type of postoperative jaundice, it is mandatory that the physician seeing a jaundiced postoperative patient review the patient's preoperative, intraoperative, and postoperative record including anesthesia and operative records, for evidence of shock, hypovolemia, inadequate urine output, etc.

This type of postoperative jaundice usually has its onset 1 to 5 days after operation and peaks after 9 to 18 days. Liver function tests often suggest cholestasis with a markedly increased bilirubin and alkaline phosphatase and only moderate transaminase elevations (600 to 1000). Azotemia and oliguria are frequent coexisting abnormalities and probably reflect the same etiologic factors affecting the kidneys. These patients usually recover unless some other complication occurs, such as renal failure, sepsis, bleeding, or myocardial infarction. The major difficulty in managing these patients is to exclude obstructive jaundice and thereby avoid unnecessary additional high-risk operations with the inherent danger of more hypoxia and hypotension. The recent development of retrograde endoscopic cholangiography[7, 47] may well have its most important clinical application in these patients. Clearly, the demonstration of a normal extrahepatic biliary system, using this nonoperative technique, will eliminate unnecessary surgical procedures in these critically ill patients.

Hepatotoxic drugs,[21] congestive heart failure,[41] sepsis,[9, 20] and the nonspecific impairment of hepatic function that occurs postoperatively,[13] are other causes of impaired postoperative hepatocellular function and jaundice. They rarely are seen in isolation and therefore present with variable liver function abnormalities. These situations are best recognized by critical attention to detail concerning medications, vital signs (including central venous pressure), and general patient care. Their treatment is simply treatment of the specific abnormality with antibiotics, digitalis, diuretics, etc., after appropriate diagnostic procedures (cultures of blood, drainage sites, wounds, electrocardiogram, chest x-rays, etc.) have been obtained.

Anesthetic hepatotoxicity is a rare clinical event occurring in approx-

imately 1 out of 10,000 patients who receive either halothane or methoxyflurane (Penthrane) anesthesia.[5, 19, 43] The pathophysiologic mechanisms responsible for the massive hepatocellular necrosis that occasionally occurs with use of these agents is unknown. It would appear initially, however, to be a direct hepatocellular injury which, for some unexplained reason, continues as a delayed hypersensitivity response.[15, 33] In the typical case,[45] unexplained fever and leukocytosis, usually with eosinophilia, develops on the second or third postoperative day. Although jaundice is delayed and may not appear for several weeks, marked transaminase elevations are seen early. Several days after the onset of the fever, the liver becomes enlarged and is tender. Hepatic encephalopathy can develop very rapidly in these cases. With massive hepatic necrosis, liver size may decrease rather than increase and this occurrence is obviously a poor prognostic sign. Prior exposure to halothane or methoxyflurane seems to accelerate the pace of jaundice and the subsequent development of hepatic encephalopathy. Because of the severe nature of these anesthetic hepatotoxicities, any history of unexplained fever, anorexia, lethargy, eosinophilia, and/or transaminase elevation following surgery with either of these agents should be an absolute contraindication to their further use in a given patient.

The liver histology of anesthetic hepatotoxicity, as determined from review of biopsy and/or autopsy material, is reported to be indistinguishable from massive hepatic necrosis (acute yellow atrophy) resulting from viral hepatitis.[34] The picture is one of diffuse panlobular hepatocellular necrosis with Kupffer cell hyperplasia, pigment phagocytosis, and occasional acidophilic "Councilman" bodies. Clearly, any patient with known preoperative hepatocellular dysfunction is at greater risk for the development of postoperative jaundice than a normal individual. Furthermore, the reported observation that a slight, clinically unimportant, transient bilirubin elevation up to 1.5 mg per 100 ml follows uncomplicated abdominal surgery and that it is unrelated to any specific anesthetic agent or operative procedure, nicely underscores this statement.[13] The mechanisms responsible for this biochemical jaundice in normal individuals postoperatively is unclear. Hepatic blood flow is reduced by 30 per cent under anesthesia, because of visceral shunting.[40] These factors may partially explain the appearance of postoperative jaundice in certain cases. Whether it is related to the similarly unexplained, but frequently observed, increase in chemical and clinical jaundice in individuals with Gilbert's disease while fasting or under stress is uncertain at present.[36]

Patients with anicteric viral hepatitis, unsuspected alcoholic hepatitis and/or well compensated cirrhosis without the usual physical findings, especially those in older age groups, are of special concern. They may complain of vague upper right quadrant epigastric or periumbilical pain described as burning, aching, or pressure and mistakenly be thought to have biliary tract or peptic ulcer disease. If these patients are operated upon, they understandably develop postoperative jaundice. Although data concerning the mortality and morbidity of surgical procedures in jaundiced patients are either nonexistent or incomplete, it

would appear that patients with clinical "hepatitis" or "hepatocellular necrosis" are poor surgical risks,[16] unlike those with predominantly "cholestatic" jaundice who seem to tolerate operations reasonably well. The reported mortality for the former group is 9.5 per cent. The incidence of major complications excluding death in this population is an additional 11.9 per cent. Thus a total of 21.7 per cent of such patients will either die or suffer a major complication such as a major pulmonary embolism, wound dehiscence, subphrenic abscess, etc. No data of a similar nature are available for those with a purely cholestatic picture.

Two forms of familial hyperbilirubinemia are exacerbated by surgical stress, infection, and fasting and should also be considered under hepatocellular mechanisms for jaundice. Gilbert's disease produces an indirect unconjugated hyperbilirubinemia. The Dubin-Johnson syndrome produces a direct reacting or conjugated hyperbilirubinemia. The latter syndrome is characterized by an inability to excrete cholecystographic dyes. Serious diagnostic and therapeutic errors can be made if the surgeon first becomes aware of this entity in a patient in the postoperative condition.

A rare but very dramatic form of postoperative jaundice is seen in cases in which the entire hepatic pedicle (blood vessels and bile ducts) are ligated at surgery. In these cases massive hepatic infarction occurs with rapidly developing intense jaundice. Transaminase levels are markedly elevated early and may fall after several days as the patient develops progressive hepatic failure and dies.

A poorly understood, occasionally seen, but often cited form of postoperative jaundice is the syndrome of idiopathic benign postoperative intrahepatic cholestasis associated with prolonged operative procedures.[39] The case reports of patients thought to have this type of postoperative jaundice, however, are complicated by many potential etiologic factors that are known to produce jaundice, such as multiple transfusions, hypotensive and hypoxic episodes, multiple hepatoxic drugs and even preexisting liver disease. The readers are referred to the original description of this syndrome[39] and can determine for themselves if it is a true syndrome.

A POSTHEPATIC DEFECT—INABILITY TO EXCRETE CONJUGATED BILIRUBIN

Jaundice occurring as a result of injury to the extrahepatic biliary tract, although uncommon, must be recognized as it is the only type of postoperative jaundice amenable to surgical correction. Obstruction, either complete and constant or partial and intermittent, is the pathologic mechanism in all cases. If not recognized early, it results in recurrent cholangitis, sepsis, and eventually biliary cirrhosis, with progressive debilitation of the patient because of combined nutritional and metabolic abnormalities.[14, 48] As might be anticipated, injuries to the extrahepatic biliary system occur most frequently after operation for cholecystitis or choledocholithiasis, but also occur following procedures for peptic

ulcer disease or other surgical procedures in the upper abdomen.[23] They usually occur in cases which require difficult dissection or blind ligature such as cases of recurrent surgery complicated by adhesions, or disturbed anatomy and/or complicated by peritonitis or abscess formation.[48] The postoperative history is often of great value in these cases.[14] A frequent sequence is the appearance of jaundice within 48 hours of operation. In such cases, the presence of copious biliary drainage from wound or drainage sites within a week is suggestive of occlusion of the common duct by ligature and subsequent perforation due to necrosis of the bile duct just proximal to the ligature. On the other hand, a large discharge of bile within hours after operation is more likely due to an unrecognized transection of a major bile duct occurring at operation.

These situations, when recognized, should be evaluated quickly, utilizing all the methods currently available,[10] which include instillation of radiopaque material into surgical drains and fistulous tracts, combined with retrograde endoscopic cholangiography[7] and upper and lower gastrointestinal series, and then early surgical repair. Intravenous and oral cholangiograms are unlikely to be of value in these patients because the level of jaundice and impaired hepatobiliary function present usually mitigates against adequate visualization with these techniques.[54] For all practical purposes, the recent development of retrograde endoscopic cholangiography[7, 47] has eliminated the need to use percutaneous transhepatic cholangiography in these situations. The method of repair at reoperation depends upon the type of bile duct injury found, type of preceding operation, and the skill of the surgeon.[14, 23, 48, 53]

Common duct stricture occurring as a consequence of the normal healing process following unrecognized ductal injury often results in a narrowed and contracted lumen which produces either progressive low-grade chronic obstruction or, more frequently, intermittent incomplete obstruction years after the initial surgical procedure.[14] The insidious development and intermittent nature of such a surgical complication usually results in greatly delayed recognition. Investigation is usually delayed until the patient has experienced several episodes of intermittent obstructive jaundice, abdominal pain suggestive or choledocholithiasis, cholangitis, or sepsis, and has some, if not signficant, irreversible hepatic injury. As in the preceding situation, but unlike the acute situation, endoscopic retrograde cholangiography[7] and intravenous cholangiography are valuable diagnostic tools. Again the method of surgical repair for these complications depends upon the anatomic circumstances present at the time of the re-exploration and the skill and experience of the surgeon—and will not be discussed here. The subject matter, however, is reviewed elsewhere.[14, 23, 48, 49]

Early postcholecystectomy common duct obstruction due to unrecognized or retained choledocholithiasis is another cause of postoperative jaundice and can occur in as many as 5 per cent of patients operated upon who have had their common ducts explored.[2, 18, 51] When present it can give rise to the typical picture of biliary colic and obstructive jaundice in the immediate postoperative period. The diagnosis,

however, may be difficult if laboratory findings are not typical or the pain and fever are masked by narcotic or antipyretic medications. Recent reports of ductal instillation with heparin,[12] cholic acid,[50] and quaternary amines[22] cite dissolution of such stones, relieving the obstruction. Cholic acid infusions is reported to be successful in as many as two thirds of the patients in which it has been tried.[50, 51] In addition, reports of forcep or basket extraction of such stones[10, 11, 25, 28] utilizing radiologic monitoring have been reported with a 90 per cent success rate. These methods will obviously reduce the frequency for which re-exploration is required. Unfortunately, they require special equipment and physicians with special skills and should still be considered experimental. Should ascending cholangitis or pronounced biliary obstruction develop, surgical intervention without delay is mandatory. In cases of retained stone without cholangitis or evidence of obstruction, nonoperative methods can be tried. However, these methods are still experimental and not generally available outside a surgical research unit. When used they are usually delayed 2 to 4 weeks to allow for wound healing and then continued for a similar period of time before reoperation is advised.[51] If such a unit is not available operation is usually delayed to allow wound healing and subsiding of inflammation. Reoperation is ultimately necessary in these cases to remove the retained stone.

Postoperative pancreatitis[52] can, on occasion, produce significant obstructive jaundice, but is usually recognizable from the clinical picture as well as determination of the serum and urinary amylase. Again, intravenous and endoscopic retrograde cholangiography are valuable diagnostic tools in such cases. As might be expected, this latter procedure is significantly more difficult and potentially dangerous in cases with suspected acute inflammatory pancreatic disease. Demonstration of an intrinsically normal extrahepatic biliary system in such cases obviates the need for re-exploration in these critically ill patients.

Finally, an unusual occurrence is postoperative cholecystitis appearing 3 to 30 days after operations unrelated to the biliary tract.[17] In over half of the reported cases, no stones were found in the gallbladder or common duct. Bacteria, however, are usually found in the bile or surrounding peritoneal fluid and gangrene of the gallbladder is not uncommon. These patients usually present with nausea, vomiting, and acute periumbilical and occasionally right upper quadrant or subscapular pain, characteristic of acute cholecystitis. As in cases of retained biliary calculi, the clinical picture can be obscured by coincidental administration of analgesics and antipyretics as well as the nature of preceding surgical procedure. As soon as the diagnosis is suspected and confirmed by appropriate methods, surgical intervention ought to be immediately initiated because of the great risk of gallbladder perforation occurring in these patients, who, as noted above, frequently have gangrene of the gallbladder.

As can be seen from the preceding discussion, postoperative jaundice is indeed a difficult diagnostic problem. It requires all the knowledge and clinical skill available to the practicing physician in order that those cases requiring additional operative therapy are identified and

those in whom surgical therapy is not indicated are spared an unnecessary and potentially dangerous additional insult.

REFERENCES

1. Barrett, P. V. D., Berk, P. D., Menkin, M., et al.: Bilirubin turnover studies in normal and pathological states utilizing bilirubinC^{14}. Ann. Intern. Med., *68*:355, 1968.
2. Bartlett, M. K., Washow, A. L., and Ottinger, L. W.: The removal of biliary duct stones. Surg. Cl. North America *54*:599, 1974.
3. Bean, W. J., Smith, S. C., and Mahoner, H. R.: Equipment for nonoperative removal of biliary tract stones. Radiology, *107*:452, 1973.
4. Burhenne, H. J.: Non-operative retained biliary stone extraction. Amer. J. Roentgen., *117*:338. 1973.
5. Carney, F. M. T., and Van Dyke, R. A.: Halothane hepatitis: A critical review. Anesth. Analg., *51*:135, 1972.
6. Corday, E., and Williams, J. H., Jr.: Effect of shock and vasopressor drugs on the regional circulation of the brain, heart, liver and kidney. Amer. J. Med., *9*:228, 1960.
7. Cotton, P. B., Blungant, L. H., Davies, G. T., et al.: Cannulation of papilla of vater via fiberduodenoscope. Lancet, *1*:53, 1972.
8. Crosby, W. H., and Howard, J. M.: The hematologic response of wounding and resuscitation accomplished by large transfusions of stored blood. Blood, *9*:439, 1954.
9. Eley, A., Hargreaves, T., and Lambert, H. P.: Jaundice in severe injection. Brit. Med. J., *10*:75, 1965.
10. Ferrucci, J. T., Jr., and Eaton, S. B., Jr.: Radiologic evaluation of obstructive jaundice. Surg. Clin. N. Amer., *54*:573, 1974.
11. Galloway, S. J.: Nonoperative treatment of retained stones in the common duct. Surg. Gynec. Obstet., *137*:55, 1973.
12. Gardner, B.: Experiences with the use of intracholedochal heparinized saline for the treatment of retained common duct stones. Ann. Surg., *177*:240, 1973.
13. Geller, W., and Tagnon, H. J.: Liver dysfunction following abdominal operations: Significance of postoperative hyperbilirubinemia. Arch. Intern. Med., *86*:908, 1950.
14. Glenn, F.: Postoperative strictures of the extrahepatic bile ducts. Surg. Obstet. Gynec., *120*:560, 1965.
15. Gottlieb, L. S., Trey, C.: The effects of fluoronated anesthetics on the liver and kidneys. Ann. Rev. Med., *25*:411–429, 1974.
16. Harville, D. D., and Summerskill, W. H. J.: Surgery in acute hepatitis. J.A.M.A., *184*:257, 1963.
17. Howard, R. J., and Delaney, J. P.: Postoperative cholecystitis. Amer. J. Dig. Dis., *17*:312, 1972.
18. Jolly, P. C.: Operative cholangiography: A case for its routine use. Ann. Surg., *168*:551, 1968.
19. Joshi, P. H., and Conn, H. O.: The syndrome of methoxyflurane associated hepatitis. Ann. Intern. Med., *80*:395, 1974.
20. Klatskin, G.: Hepatitis associated with systematic injection. *In* Schiff, L., ed.: Disease of the Liver. Philadelphia, J. B. Lippincott Co., 3rd ed., 1969, pp. 602–644.
21. Klatskin, G.: Toxic and drug-induced hepatitis. *In* Schiff, L., ed.: Disease of the Liver. Philadelphia, J. B. Lippincott Co., 3rd ed., 1969, pp. 498–601.
22. Lahana, D. A., Bonouris, G. G., and Schoenfield, L. J.: Gallstone dissolution in vitro by bile acids, heparin and quaternary amines. Surg. Obstet. Gynec., *138*:683, 1974.
23. Longmire, W. P., Jr.: Early management of injury to the extrahepatic biliary tract. J.A.M.A., *195*:623, 1966.
24. McMichael, J.: The oxygen supply of the liver. Quart. J. Exper. Physiol., *27*:73, 1937.
25. Magarey, C. J.: Nonsurgical removal of retained biliary calculi. Lancet, *1*:7708, 1971.
26. Maizels, M., Prankerd, T. A. J., and Richards, J. D. M.: Haematology in diagnosis and treatment. London, Bailliere Tindall and Cassell, 1968, pp. 142–184.
27. Mazariello, R.: Removal of residual biliary tract calculi without reoperation. Surgery, *67*:566, 1970.
28. Mazariello, R.: Review of 220 cases of residual biliary tract calculi treated without reoperation. Surgery, *73*:289, 1973.
29. Mollison, P. L.: Blood Transfusion in Clinical Medicine. Philadelphia, F. A. Davis Co., 3rd ed., 1962.
30. Moon, V. H.: The pathology of secondary shock. Amer. J. Path., *24*:235, 1948.

31. Morgenstern, L.: Postoperative Jaundice. *In* Schiff, L., ed.: Disease of the Liver. Philadelphia, J. B. Lippincott Co., 3rd ed., 1969, pp. 1036–1050.
32. Nunes, G., Blaidsdell, W., and Margaretten, W.: Mechanism of hepatic dysfunction following shock and trauma. Arch. Surg., *100*:546, 1900.
33. Paronetto, R., Papper, H.: Lymphocyte stimulation induced by halothane in patients with hepatitis following exposure to halothane. New Eng. J. Med., *283*:277, 1970.
34. Peters, R. L., Edmondson, H. D., Reynolds, R. B., et al.: Hepatic necrosis associated with halothane anesthesia. Amer. J. Med., *47*:748, 1969.
35. Popper, H., and Schaffner, F.: Hepatocellular Degeneration and Necrosis: Structure Alterations in the Liver. New York, McGraw Hill Book Co., 1957.
36. Redeker, A. G., Richard, D., and Felsher, B. F.: The reciprocal relationship between calorie intake and degree of hyperbilirubinemia in Gilbert's syndrome. Gastroenterology, *58*:303, 1970.
37. Rowland, L. P., and Penn, A. S.: Myoglobinuria. Med. Clin. N. Amer., *56*:1233, 1972.
38. Schiff, L., and Billings, B. H.: Jaundice. *In* Schiff, L., ed.: Disease of the Liver, Philadelphia, J. B. Lippincott Co., 3rd ed., 1969, pp. 228–267.
39. Schmid, M., Hefti, M. L., Gattiker, R., et al.: Benign postoperative intrahepatic cholestasis. New Eng. J. Med., *272*:545, 1965.
40. Shackman, R., Graker, I. G., and Melrose, D. G.: The haemodynamics of the surgical patient under general anesthesia. Brit. J. Surg., *40*:193, 1953.
41. Sherlock, S.: The liver in heart failure: relation of anatomical, functional and circulatory changes. Brit. Heart J., *13*:273, 1951.
42. Shorey, J., Schenker, S., and Combes, B.: Hepatic transport in shock hypoxia. Clin. Res., *16*:292, 1968.
43. Summary of the National Halothane Study, Report of the Subcommittee of the National Halothane Study of the Committee of Anesthesia, National Academy of Science, National Research Council, J.A.M.A., *197*:775, 1966.
44. Topley, E., and Clarke, R.: Anemia of trauma. Blood, *11*:357, 1956.
45. Trey, C., Lipworth, L., and Davidson, C. S.: The clinical syndrome of halothane hepatitis. Anesth. Analg., *78*:1033, 1969.
46. Umansky, I: Blood groups II, Pathology and Transfusion Therapy in Hematology. Edited by W. S. Beck. Cambridge, The MIT Press, 1973, pp. 248–249.
47. Vennes, J. A., Jacobson, J. R., and Silvis, S. E.: Endoscopic cholangiography for biliary system diagnosis. Ann. Intern. Med., *80*:61, 1974.
48. Warren, K. W., and Jefferson, M. F.: Prevention and repair of strictures of the extrahepatic bile ducts. SURG. CLIN. N. AMER., *53*:1169, 1973.
49. Warren, K. W., McDonald, W. M., and Kune, G. A.: Bile Duct Strictures: New Concepts in the Management of an Old Problem. *In* Irvine: W. T., ed.: Modern Trends in Surgery. Butterworth & Co., London, 2nd ed., 1966, pp. 86–110.
50. Way, L. U., Admirand, W. H., and Dunphy, J. E.: Management of choledocholithiasis. Ann. Surg., *176*:347, 1972.
51. Way, L. W.: Retained common duct stones. Surg. Clin. N. Amer., *53*:1139, 1973.
52. Weinstein, B. R., Korn, R. J., and Zimmerman, H. J.: Obstructive jaundice as a complication of pancreatitis. Ann. Intern. Med., *58*:245, 1963.
53. Williams, G. R.: Experience with surgical reconstruction of the hepatic ducts. Ann. Surg., *179*:540, 1974.
54. Wise, R. E.: Intravenous cholangiography. *In* Morgulis, A. R., and Burchenne, H. J., eds.: Alimentary Tract Roentgenology. St. Louis, C. V. Mosby Co., 1973, pp. 1291–1302.

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Evaluation of the Patient with Suspected Extrahepatic Biliary Obstruction

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The Greek word *ikteros* is derived from the word *ictides*, a species of ferret with bright yellow eyes. Skin and, to an even greater degree, the sclerae have a particular affinity for circulating bilirubin. When the serum concentration of conjugated and/or unconjugated bilirubin exceeds 2.5 to 3.0 mg per 100 ml, clinical jaundice is usually apparent. The causes of jaundice are diverse, are often difficult to identify using clinical criteria alone, and usually require specific therapy for their resolution. A patient with jaundice secondary to hepatitis may succumb to a diagnostic laparotomy;[6] another patient with jaundice secondary to neoplastic extrahepatic obstruction may eventually succumb because of an unnecessarily long delay in diagnosis. The diagnostic evaluation should be expeditious, but not precipitous. Broadly speaking, the causes of jaundice may be categorized as: hemolytic, hepatocellular, and obstructive (intrahepatic and extrahepatic). Appropriate therapy demands identification of the underlying disease mechanism. A comprehensive history and physical examination can occasionally lead to the correct diagnosis; but more often than not, the clinician must rely heavily upon various laboratory, radiologic, endoscopic, and radioisotopic studies.

PHYSIOLOGY

Two hundred and fifty to 300 mg of bilirubin are formed daily, predominantly from the catabolism of senescent red blood cells, in the adult reticuloendothelial system.[18] This water-insoluble bilirubin is firmly bound to plasma albumin in which state it is circulated to the liver. The hepatocyte has a strong affinity for bilirubin. Intracellular bilirubin is conjugated with glucuronic acid (requiring the enzyme glucuronyltransferase), and once conjugated, bilirubin is actively secreted against a concentration gradient into the biliary canaliculae and, ultimately, into the extrahepatic biliary system. Jaundice may be the result of increased

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Table 1. *Medications Associated with Hepatic Dysfunction*

Organic arsenicals*	Nitrofurantoin*
Azathioprine	Norethandrolone*
Chloramphenicol*	Para amino salicylic acid* †
Chlorpropamide	Phenindione
Erythromycin estolate* †	Phenothiazines*
Isoniazid†	Phenylbutazone
6 Mercaptopurine	Propylthiouracil* †
Methimazole* †	Sulfonamides* †
Methyldopa†	Tetracycline†
Methyl testosterone*	

*Cholestatic
†Hepatocellular injury

heme catabolism (hemolysis), an impaired uptake of bilirubin by the hepatocyte (? Gilbert's syndrome), a deficiency of glucuronyl-transferase (Crigler-Najjar and ? Gilbert's syndromes), a defect in the active secretion of conjugated bilirubin into the canaliculae (Dubin Johnson syndrome), intrahepatic cholestasis (viral hepatitis, portal cirrhosis, fatty metamorphosis, primary biliary cirrhosis, drug reaction) or extrahepatic biliary obstruction (choledocholithiasis, benign biliary stricture, biliary and periampullary neoplasms, and extrinsic compression). The hepatocyte is capable of excreting bile into the biliary tree at a pressure head of 35 cm of saline. A normal sphincter of Oddi will spontaneously relax when the intrabiliary pressure exceeds 15 cm of saline.[7] Any intrinsic or extrinsic lesion compromising sphincteric function will lead to the retention of conjugated bilirubin and the appearance of clinical jaundice, when the sphincteric passage pressure exceeds 35 cm of saline.

CLINICAL PRESENTATION

With the exception of biliary colic, there are few symptoms in the jaundiced patient that are of great diagnostic value. Malaise, weight loss, anorexia, pruritus, and a decreased desire for cigarette smoking are common expressions of a variety of hepatobiliary disorders. Choluria and acolic stools suggest but are not diagnostic of biliary obstruction. An antecedent history of fried and fatty food intolerance is consistent with the diagnosis of cholelithiasis but is not pathognomonic. A careful history of drug exposure is mandatory. A list of medications potentially causing jaundice is presented in Table 1.[13, 16, 21]

On physical examination, jaundice can usually be differentiated from hypercarotinemia by the absence of scleral pigmentation in the latter condition. Gynecomastia, pectoral alopecia, palmar erythema, telangiectasia, and testicular atrophy are all stigmata of advanced cirrhosis. Liver and spleen size with or without tenderness, the presence or absence of a palpable gallbladder (Courvoisier's sign) or other intra-abdominal masses should be noted. The stool should be examined for occult blood.

LABORATORY AND RADIOLOGIC ASSESSMENT

Appropriate laboratory data usually play a critical role in establishing the cause of jaundice. The characterization of hyperbilirubinemia by fractionation into direct and indirect reacting bilirubin is helpful when one or the other fraction grossly predominates. Indirect hyperbilirubinemia is more frequently associated with hemolytic or hepatocellular jaundice, direct hyperbilirubinemia with cholestatic jaundice or extrahepatic biliary obstruction. SGOT and LDH values usually reflect the structural and functional integrity of the hepatocyte, whereas alkaline phosphatase levels may reflect the structural and functional integrity of the biliary ductal epithelium. Albumin and prothrombin levels are indices of hepatic synthetic capacity. Antimitochondrial antibodies are detectably elevated in most patients with primary biliary cirrhosis but may be falsely elevated in one quarter of patients with chronic active hepatitis or postnecrotic cirrhosis. In drug-induced and viral hepatitis and extrahepatic biliary obstruction, antimitochondrial antibodies are not detectable.[19]

If, at this point in the patient's evaluation, biliary obstruction is suspected but one cannot differentiate between intrahepatic cholestasis and extrahepatic biliary obstruction, a variety of radiologic studies are available. The upper gastrointestinal series or hypotonic duodenogram may detect periampullary or pancreatic pathology but the diagnostic yield, especially of curable lesions, is low.[3, 4] In the jaundiced patient, oral cholestography is useless and, unless the bilirubin is less than 5 mg per 100 ml, intravenous cholangiography with tomography similarly will fail to visualize the biliary tree.

In the majority of jaundiced patients, the diagnosis can be established by conventional clinical, laboratory and radiologic procedures; however, 20 per cent remain enigmatic. Over the past decade, a number of invasive and noninvasive procedures visualizing the biliary tree have been designed to facilitate or obviate a subsequent diagnostic laparotomy. Percutaneous transhepatic cholangiography, performed under local anesthesia, can directly visualize the biliary tree proximal to the site of obstruction.[5] (Fig. 1). It is useful in differentiating between obstructive and non-obstructive jaundice, in determining the cause of obstructive jaundice and in localizing the level of obstruction. Optimally, the patient should be jaundiced for at least 2 weeks to permit adequate ductal dilatation. By this technique the biliary tree is visualized in over 80 per cent of patients with ductal obstruction, and in roughly 50 per cent of patients without ductal obstruction. If after five attempts the ductal system cannot be cannulated and visualized, the patient most probably has nonobstructive jaundice.[15]

If an obstructed biliary tree is demonstrated by this technique, a laparotomy for decompression is usually essential within hours of this procedure. A variation of this is transjugular, transhepatic cholangiography,[20] which has enjoyed limited use. For this technique a cannula is

Figure 1. Percutaneous transhepatic cholangiogram in a patient with extrahepatic biliary obstruction secondary to a cholangiocarcinoma of the proximal common bile duct. CATH, teflon catheter; RHD, right hepatic duct; LHD, left hepatic duct; CBD, common hepatic duct; CDR, cystic duct remnant; CA, obstructing cholangiocarcinoma.

inserted via the jugular vein into the hepatic vein and then advanced into the hepatic parenchyma. Resultant bacteremia can usually be avoided by pretreating the individual with systemic antibiotics. Contraindications to either of these two techniques include the possibility of lymphoma, liver metastasis, liver abscess, hydatid cyst disease, and acute cholangitis.

More recently duodenoscopy with retrograde choledochopancreatography has been described.[2, 9, 10, 11] It is technically difficult to perform. The incidence of gram-negative septicemia and hyperamylasemia has been acceptably low. When successfully performed, this procedure can document the presence of extrahepatic obstruction, can localize the nature and site of obstruction, and can possibly obtain cells or tissue for cytologic or histologic evaluation (Fig. 2). As instrumentation improves and the number of trained endoscopists increases, this diagnostic procedure will enjoy considerably greater popularity than at present.

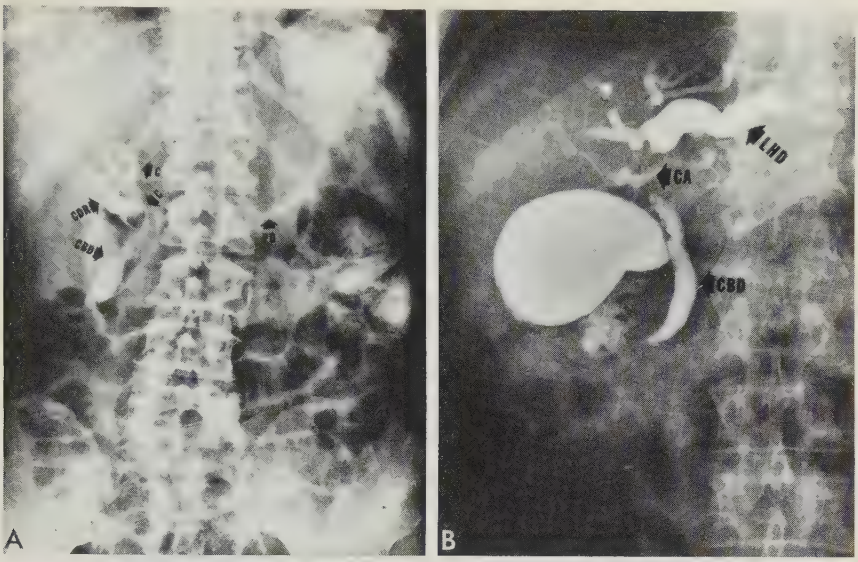

Figure 2. *A*, Retrograde choledochopancreatogram in a patient with intermittent jaundice and biliary colic and a previous cholecystectomy. CDR, cystic duct remnant; CBD, common bile duct; C, calculus; PD, pancreatic duct.

B, Retrograde choledochopancreatogram in a patient with painless jaundice. LHD, dilated left hepatic duct; CA, obstructing cholangiocarcinoma; CBD, common bile duct.

Other approaches to the biliary tree have been reported and include (1) laparoscopy with transhepatic cholecystocholangiography and (2) limited laparotomy under local anesthesia. Laparoscopy with transhepatic cholecystocholangiography has the theoretical advantages of being able to directly cauterize the hepatic puncture site, and of not requiring a dilated intrahepatic ductal system for successful biliary visualization by virtue of passing the cannula through the hepatic substance into the gallbladder under direct visualization. Limited laparotomy under local anesthesia facilitating transhepatic cholangiography, liver biopsy, and omentoportography represents an integrated diagnostic approach with a reportedly high diagnostic yield and limited morbidity.[17] Both these modalities will require a more widespread use before their usefulness can be adequately determined.

The combination of selective visceral arteriography and percutaneous transhepatic cholangiography has been reported to be diagnostic in over 90 per cent of jaundiced patients.[8, 15] In addition to localizing the site and nature of the biliary obstruction, hepatic metastasis greater than 2 cm in diameter can usually be visualized and, on the venous phase of the superior mesenteric arteriogram, the integrity of the superior mesenteric vein can be evaluated, determining resectability (Fig. 3).

Liver scans are useful in evaluating liver size, liver shape and space occupying hepatic lesions. This technique is reported to be 80 per cent

Figure 3. Venous phase of a superior mesenteric arteriogram in a patient with an extensive carcinoma of the head of the pancreas and painless jaundice. PV, portal vein; OBS, extensive pancreatic carcinoma; COL, extensive superior mesenteric venous collaterals; SMV, superior mesenteric vein.

reliable in detecting lesions greater than 2 cm in diameter. The clearance of radioactive rose bengal by the liver has been of limited value in helping to differentiate between obstructive and nonobstructive jaundice.[14] On interpreting filling defects in the liver scan, it is often impossible to differentiate between dilated bile ducts, neoplasia, abscess, or regenerative or sclerotic tissue.

A closed needle liver biopsy should only be attempted if it seems unlikely that there is significant extrahepatic biliary obstruction.[12] Otherwise, significant bile leakage may ensue, necessitating an unplanned laparotomy and a less than optimal biliary bypass procedure.

CONCLUSION

In most patients, obstructive jaundice can be differentiated from intrahepatic cholestatic jaundice employing conventional clinical, radio-

logic, and laboratory techniques. Roughly 20 per cent of these patients will remain without a diagnosis. During the past decade, several invasive and noninvasive techniques for visualizing the biliary tree have been developed, increasing the diagnostic yield to over 90 per cent. The combination of selective visceral arteriography and percutaneous transhepatic cholangiography is currently the preferred approach. Duodenoscopy with retrograde choledochopancreatography, as an alternative approach, will become increasingly utilized in the near future. An exploratory laparotomy for jaundice of *undetermined* etiology should not be undertaken without first performing one or the other of the above procedures.

REFERENCES

1. Berci, G., Morgenstern, L., Shore, J. M., et al.: A direct approach to the differential diagnosis of jaundice. Amer. J. Surg., *126*:372, 1973.
2. Blumgart, L. H., Salmon, P. R., and Cotton, P. B.: Endoscopy and retrograde choledochopancreatography in the diagnosis of the patient with jaundice. Surg. Gynec. Obstet., *138*:565, 1974.
3. Bree, R. L., and Flynn, R. E.: Hypotonic duodenography in the evaluation of choledocholithiasis and obstructive jaundice. Amer. J. Roentgen., *116*:309, 1972.
4. Eaton, S. B., Benedict, K. T., and Ferrucci, J. T., Jr.: Hypotonic duodenography. Radiol. Clin. N. Amer., *8*:125, 1970.
5. Ham, J. M., Sorby, W. A., Colman, J. V. L., et al.: Percutaneous transhepatic cholangiography. Surg. Gynec. Obstet., *135*:784, 1972.
6. Harville, D. D., and Summerskill, D. M.: Surgery in acute hepatitis. J.A.M.A., *184*:257, 1963.
7. Hopton, D., and White, T. T.: An evaluation of manometric operative cholangiography in 100 patients with biliary disease. Surg. Gynec. Obstet., *133*:949, 1971.
8. Kaplan, M. S., Juler, G. L., Stanton, W., et al.: Rapid and accurate preoperative diagnosis of obstructive jaundice. Arch. Surg., *108*:825, 1974.
9. Kasugai, T., Kuno, N., Kobayashi, S., et al.: Endoscopic pancreatocholangiography. I. The normal endoscopic pancreatocholangiogram. Gastroenterology, *63*:217, 1972.
10. Kasugai, T., Kuno, N., Kobayashi, et al.: Endoscopic pancreatocholangiography. II. The pathological endoscopic pancreatocholangiogram. Gastroenterology, *63*:227, 1972.
11. Katon, R. M., Lee, T. G., Parent, J. A., et al.: Endoscopic retrograde cholangiopancreatography. Amer. J. Dig. Dis., *19*:295, 1974.
12. Kelley, M. L., Jr., Mosenthal, W. T., and Milne, J.: Bile leakage following Meghini needle liver biopsy. J.A.M.A., *216*:333, 1971.
13. Lamont, J. T., and Isselbacher, K. J.: Postoperative jaundice. New Eng. J. Med., *288*:305, 1973.
14. Olsson, R., and Bjurstam, N.: Radioactive rose bengal test in the differential diagnosis of jaundice. Surg. Gynec. Obstet., *136*:273, 1973.
15. Redman, H. C., Reuter, S. R., and Joseph, R. R.: Roentgenographic evaluation of patients with suspected obstructive jaundice. Surg. Gynec. Obstet., *131*:1100, 1970.
16. Spellberg, M. A.: Intrahepatic cholestasis vs. posthepatic jaundice: Methods of diagnosis. Med. Clin. N. Amer., *48*:53, 1964.
17. Strack, P. R., Newman, H. K., Lerner, A. G., et al.: An integrated procedure for the rapid diagnosis of biliary obstruction, portal hypertension and liver disease of uncertain etiology. New Eng. J. Med., *285*:1225, 1971.
18. Thompson, R. P. H.: Recent advances in jaundice: Physiology. Brit. Med. J., *1*:223, 1970.
19. Walker, J. G., Doniach, D., Roitt, I. M., et al.: Immune studies in liver disease. *In* Read, A. E.: The Liver. London, Butterworths, 1967.
20. Weiner, M., and Hanaffe, W. N.: A review of transjugular cholangiography. Radiol. Clin. N. Amer., *8*:53, 1970.
21. Witcomb, F. F., Trey, C., and Braasch, J. W.: Preoperative preparation of the jaundiced patient. SURG. CLIN. N. AMER., *50*:663, 1970.

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Nuclear Medicine Studies in the Diagnosis of Diseases of the Liver, Pancreas, and Spleen

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Nuclear medicine studies of the liver, spleen and pancreas have their major clinical applications in the evaluation of structure. The studies are based on static imaging, the abnormal study being one that differs from the normal in the size, shape, or position of the organ, or in the uniformity of distribution of the radioisotope within it. In a number of conditions, these imaging techniques have added a new and highly reliable method of diagnosis; in some, they can serve as screening or confirmatory studies; in others, their role is more limited or still in dispute. In the sections that follow, my goals are to: (1) provide a brief explanation of the drugs and instruments on which the studies are based; (2) discuss the clinical setting in which radionuclide studies are useful, (3) present the particular advantages of these studies as well as their limitations.

LIVER

An important consideration in evaluating radiopharmaceuticals is the radiation dose delivered to the patient. This radiation dose can be reduced by using a compound with one or both of the following properties: a short effective half-life in the patient and no beta particle emission in its decay process. Radiopharmaceuticals for studying the liver fall into two classes, each one removed from the blood by one of the two major cellular components of the liver, the polygonal cell and the reticuloendothelial cell (RE cell). The compounds in the first class allow visualization of the polygonal cells and the biliary tree. Among them only iodinated rose bengal has proven clinically useful. Up to now, ^{131}I,

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which gives off multiple beta particles in its decay, has for practical purposes been the only iodine isotope suitable for labeling the rose bengal. ^{131}I rose bengal is used primarily to investigate those situations in which polygonal cell function and biliary tree patency are in question.

A variety of colloidal preparations have been used for demonstration of the functioning RE cell component. One of the first was colloidal gold 198 (physical half life = 2.7 days, emits beta particles). Since colloidal particles, once trapped, remain in the liver (biological half-life is infinity) absence of beta emission and a short physical half-life are especially desirable in this class of compounds. At this time, colloidal preparations of technetium 99m (physical half-life, 6 hours; no beta emission) and indium 113m (physical half-life, 1.7 hours; no beta emission) are widely used.

Radionuclide imaging is done with two types of instruments. The rectilinear scanner consists of a single sodium iodide crystal (most commonly 5 inches in diameter) which scans back and forth over the patient, building up the image point by point and line by line. The gamma camera consists of a single stationary crystal approximately 12 inches in diameter. It constructs the image over the entire area simultaneously, continually adding detected information to all points until sufficient data has been accumulated throughout the area. The gamma camera can be used to produce an image of the static distribution of the radioactivity or a series of images that show the changing distribution of the radioactivity over time.

The thickness of the liver makes it essential to obtain multiple views. At the University of Pittsburgh, the routine study with either instrument consists of anterior, lateral, and posterior images; an anterior oblique view is added when the gamma camera is used.

There are several ways in which liver pathology is reflected in the liver scan: (1) The focal defect, either single or multiple, represents an area where normal liver tissue has been replaced by nonfunctioning tissue or displaced by a fluid collection (Fig. 1). This type of defect may be completely surrounded by functioning tissue which makes it easier to detect, or it may be located along a margin of the organ where its presence may be mistaken for a variation in normal contour. (2) Heterogenous distribution of radioactivity suggests a process which has diffusely replaced functioning tissue. (3) When a radiocolloid is used, an increase in the amount of radioactivity present in the RE cells of the spleen and bone marrow indicates a decrease in RE cell function in the liver; this is usually associated with diffuse parenchymal pathology.

The several causes of focal cold area on the liver scan include primary or metastatic tumor, abscess, traumatic rupture or hematoma, and cyst. Subhepatic or subphrenic abscesses may involve the liver, and masses arising in nearby organs such as the kidney, adrenal, pancreas, or stomach may either extend into the liver or produce abnormalities of contour by pressure alone (Figs. 2, 3 and 4).

Until recently, subsequent steps in evaluating the nature of the cold area were intrusive: needle biopsy or laparotomy. There are now two ways to narrow the differential diagnosis by newer nuclear medicine

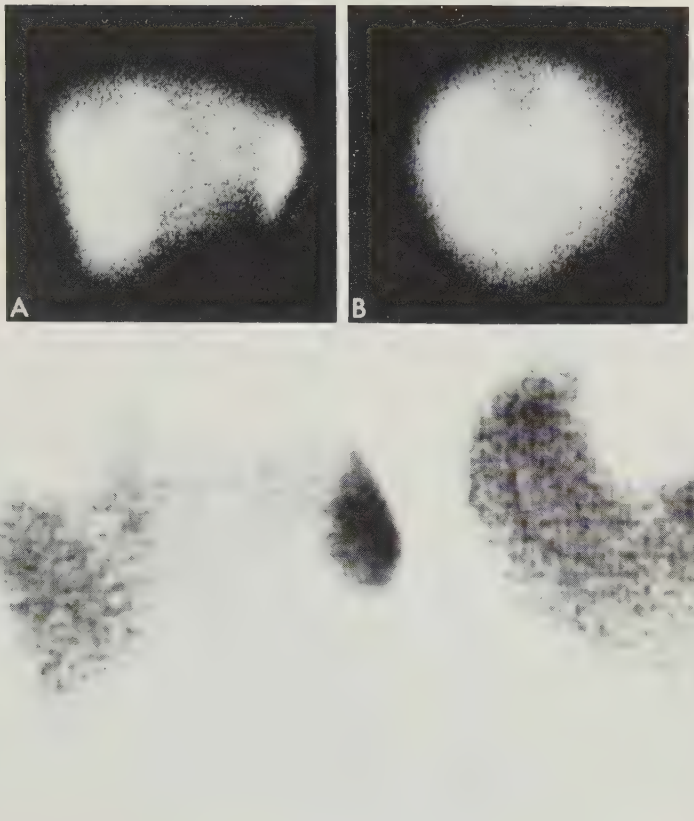

Figure 1. *A* and *B*, Anterior and right lateral camera images in a 38 year old woman showing a focal defect in the right lobe associated with carcinoma of the breast resected 4 years earlier; *C* and *D*, progression of lesion 11 months later.

Figure 2. Anterior camera image in a 54 year old man reveals multiple focal defects; carcinoma of the lung with lymphangitic spread had been diagnosed 2 months earlier.

imaging studies. One is based on the degree of vascularity of the liver abnormality relative to surrounding liver tissue. This can be assessed by sequential imaging of the liver following intravenous injection of a bolus of a radioactive drug; this study is often called an intravenous angiogram. A cyst, abscess, or hematoma, of course, is an avascular lesion. Tumors possess differing blood supplies relative to the normal liver. Most hepatomas have moderate to marked increased flow in comparison with the surrounding organ, unless significant necrosis has developed. Unfortunately, metastatic carcinoma does not present a consistent pattern and may appear as an area of decreased, increased, or normal vascularity. This study is particularly useful in differentiating the pseudotumor of cirrhosis from hepatoma, and in separating hepatocellular carcinoma from abscess or cyst. In countries such as Taiwan, in which hepatoma and amebic abscess are relatively common conditions, the intravenous angiogram has proven a valuable study.[7, 40, 74]

Gallium-67, first introduced to assist in staging lymphomas, has been found to localize in a number of tumors and in abscesses. Based on this property, gallium-67 imaging of the liver with focal defect has helped to differentiate primary liver tumor or abscess from pseudomass in cirrhosis or from a cyst.[39, 65] In addition, peripheral lesions, which often are hard to delineate as cold areas with radiocolloids since they may interfere only minimally with the function of adjacent tissue, may be seen more easily as an area of increased concentration of radiogallium (Fig. 5). The possibility of abscess is a contraindication to needle biopsy. Concentration of radiogallium in such a lesion can confirm the diagnosis of abscess (Fig. 6).

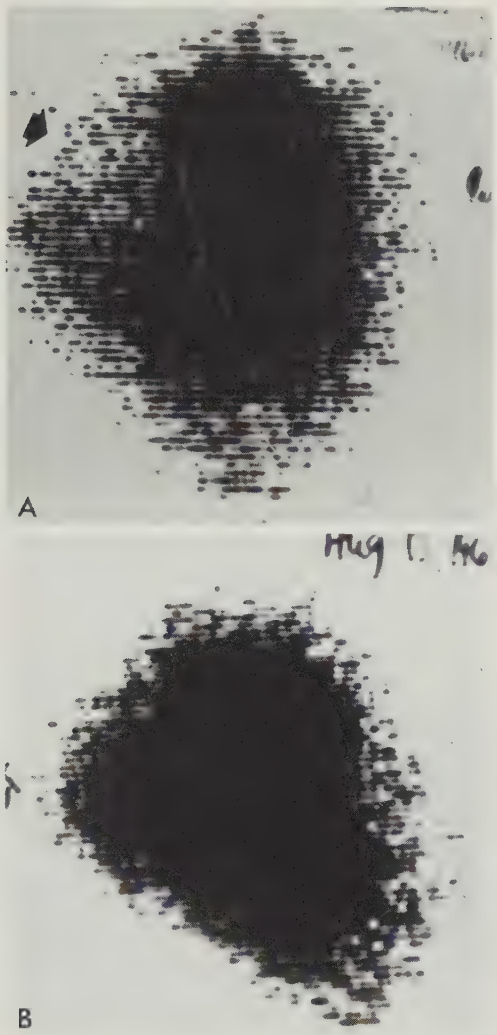

Figure 3. *A*, Lateral rectilinear scan in a 36 year old man 2 weeks following blunt trauma to the right upper quadrant from an automobile steering wheel; the patient suffered a linear rib fracture. He presents at this time with low grade fever and an elevated white count. *B*, A repeat study 6 weeks later shows that the intrahepatic hematoma has resolved; the patient is asymptomatic.

Figure 4. *A*, Anterior rectilinear scan in a 47 year old man with a 2 week history of fever and abnormal liver function tests on 12/26/72. *B*, Repeat study done 2 months after surgical drainage and partial right lobectomy for liver abscess.

Diffuse irregularity of uptake within the liver is most often associated with parenchymal disease,[21] but can also be seen with infiltrative processes such as lymphoma or granulomatous disease. Less commonly, it is seen in metastatic carcinoma. Cirrhotic process with pseudotumor is the more likely diagnosis when a focal defect is associated with diffuse heterogeneity or with significant extrahepatic concentration of radiocolloid. Nevertheless, there is no substitute for diagnosis based on histologic examination in cases where the clinical picture or laboratory findings are not consistent with the pattern seen in the scan.

The most common reason for requesting a liver scan is to determine whether metastatic disease is present. More than a third of patients with a primary carcinoma in the abdomen, usually colorectal, have metastatic liver disease at the time of exploration.[8] That the presence of metastatic liver disease has an ominous effect on survival is well recognized.[4, 20] On the other hand, it has been reported that fully half of 55 patients alive 9 years after radical colon surgery had tumor cells in the portal vein at the time of the original operation.[6] The experience of this group suggests that local metastatic disease is amenable to therapy if detected. But if it is not detected, or is not localized, then the outlook for the patient is poor no matter what the results of the primary surgery. The development of aggressive surgical techniques and of chemotherapy has made accurate preoperative diagnosis of liver metastases critical.

Of various approaches to the examination of the liver, all have been shown to misdiagnose a significant number of patients. Ahsen and Pickrin[4] found in their autopsy series that 40 per cent of the diseased livers were normal in size. Almost half of one group of patients with confirmed

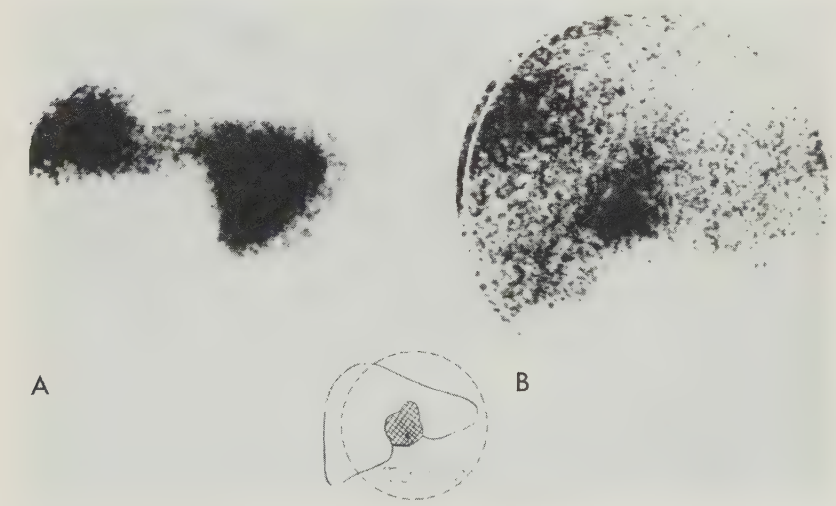

Figure 5. Liver scans in alcoholic cirrhosis with hepatoma. *A*, Colloid scan with a large defect on the inferior margin extending into the left lobe. *B*, Gallium-67 study showing localization where part of the cold area is actually a hepatoma. (*From* Lomas, F., et al.: New Eng. J. Med., 268:1323, 1972, with permission.)

Figure 6. This 70 year old woman with rheumatic heart disease had undergone cholecystotomy with removal of stones 7 years previously. She was admitted with fever and sweats. Blood culture was positive for fusiform bacteria. *A*, Tc 99m colloid scan showed an area of slight decrease in activity in the inferior half of the left lobe. *B*, A gallium-67 scan shows two areas of concentration of radioactivity; surgery revealed multiple small abscesses in the left lobe of the liver. Courtesy of Dr. Gilbert Isaacs, Montefiore Hospital, Pittsburgh.

positive scans had impalpable livers.[70] Individual liver function tests have low reliability.[17, 27] The incidence of false-negative laboratory test results has been as much as four times greater than that of the scan.[27] When abnormality in two or more liver function tests is used as a criterion, however, the sensitivity increases markedly.[17] Nevertheless, even with multiple liver function tests, results have been normal in as many as half of patients with metastatic liver disease.[70] Even surgical palpation and inspection cannot be accepted as the final arbiter of the presence or absence of the disease. The Roswell Park review found that in 11 per cent of the abnormal livers, lesions were not visible on the surface or palpable.[4] In another 4 per cent, lesions were on the surface in locations not accessible to the surgeon's hand. In a group of 46 patients with colorectal carcinoma without clinical or laboratory evidence of liver disease, 8 were shown to have tumorous livers at operation or autopsy.[20] One of these not diagnosed at operation had a positive scan.

The overall diagnostic accuracy of liver scanning for tumor (total number of correct diagnoses divided by the total number of studies done) has been reported to be between 70 and 90 per cent. This variation poses a problem in attempting to assess the value or reliability of the liver scan in patient management.[18] Assessment of diagnostic accuracy from any one institution may be affected by: (1) the selection of the patient population; (2) clinical decisions which determine the frequency and nature of biopsy and surgical correlations with scan diagnosis; and (3) the particular characteristics of the physician interpreting the scan.[11, 41] As a consequence, individual authors often draw conflicting conclusions about the usefulness of hepatic scanning.[18, 43] It is important to note that a similar problem exists in evaluating physical examination,[59, 61] liver function tests,[17, 60] and surgical exploration.[20, 59]

What then are the particular strengths of liver scanning in the patient with possible metastatic disease in the liver? (1) It is a noninvasive method of screening certain groups of patients prior to undertaking definitive therapy. In colorectal and breast carcinoma, both primary lesions with a high risk of producing metastatic liver disease, a significant number of patients scanned have had liver involvement undetected by other means.[20, 36] Patients with a normal size liver, an impalpable liver, or normal liver function tests have all been found with liver metastases in a significant number of cases.[4, 28, 70] It is singularly disheartening to encounter obvious metastatic liver disease in a patient who has recently completed therapy for the primary disease, whether this be radiation therapy, drug therapy, or surgical therapy. (2) The scan allows an estimate to be made of the extent of the liver disease, which can be used as a guide to treatment.[60] (3) It is a graphic way to establish a baseline from which to follow a patient's response to treatment. As such it can provide evidence of the success or failure of a given regimen before clinical changes occur (Figs. 1*A* to *D*). It should not be forgotten however, that false-positive and false-negative results do occur and that attempts should be made to confirm the scan findings to the extent justified by the individual case. When biopsy confirmation is sought, the

Table 1. *Decreasing Mortality in Patients with Liver Abscess over the past 50 Years*

GRANT ET AL.[32]		BLOCK ET AL.[12]		ALTEMEIER ET AL.[5]	
Time Period	Mortality	Time Period	Mortality	Time Period	Mortality
prior to 1938	75%	1923 to 1961	70%	first 5 years	80%
1938 to 1960	50%	1962 to 1965	9%	second 5 years	82%
1960 to 1965	15%			most recent 5 years	28%
current	0%				

positive yield can be increased when the liver scan is used to guide the placement of the needle.

Hepatic imaging has had a striking impact on the diagnosis and treatment of the patient with abscess in and around the liver. The diagnosis of liver abscess, whether pyogenic, parasitic, or mycotic, can be difficult on clinical evidence until late in the disease.[1, 32] Increasing clinical suspicion of this diagnosis and the use of antibiotics have not significantly affected mortality rates. Failure to drain a liver abscess has almost invariably been fatal.[5] Adequate surgical drainage, on the other hand, has reduced mortality to 10 to 25 per cent. Table 1 illustrates how the prognosis of liver abscess has changed over the years at three institutions. In each one, the surgeons attributed the difference to the liver scan, calling it the single most useful aid and the major factor in reducing mortality[5, 12, 32] (see Figs. 4 and 6).

Visceral abscesses are a very common complication in chronic granulomatous disease of childhood (CGD). The diagnosis of liver abscess in children with this condition is especially difficult because of chronic infection elsewhere in the body. When the diagnosis is suspected, a scan should be obtained promptly; when positive, it is an indication for surgical exploration (Fig. 7). Recurrence of the abscess is likely unless the involved part of the liver is completely excised.[57]

Liver and lung scans done at the same time can be a powerful diagnostic tool in evaluating the patient with a possible subphrenic abscess.[15, 16] The liver and lung can be imaged on the same film in multiple views using different radiopharmaceuticals labeled with the same radioisotope, technetium 99m. Separation of the liver and lung, often seen best in the right lateral view, indicates the presence of a fluid collection between the liver and the lung. It may be due to empyema in the right hemithorax or a subphrenic abscess; either may have extended into the liver (Fig. 8). The gallium-67 study is a further aid in localizing abscesses in this area and defining their extent.

Trauma to the abdomen is being seen with sharply increasing frequency in the civilian population. Damage to the liver is said to occur in 5 to 10 per cent of cases of nonpenetrating trauma, about half as often as laceration of the spleen (see below).[46] Mortality can be reduced by aggressive surgical management.[67] The prompt use of the liver scan will allow the diagnosis of hepatic injury to be made earlier. The findings on the scan together with the patient's condition will determine what

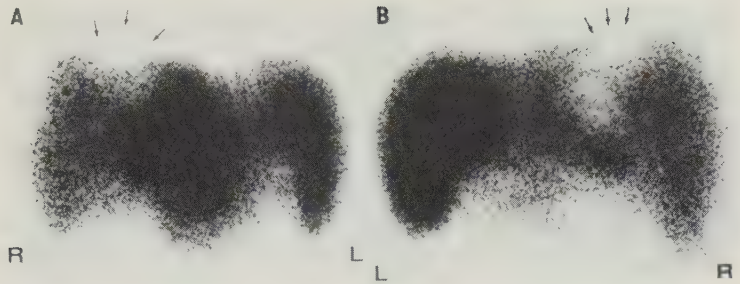

Figure 7. A 7 year old boy was admitted with a history of fever and vomiting; chronic granulomatous disease had been diagnosed at age 28 months. He had had a number of previous admissions with lung and skin infections. This time he had fever and liver tenderness. Liver scan shows a large filling defect; an abscess (Staph. aureus) was drained and excised. (*From* Preimesburger, K., and Goldberg, M.: Radiology, *110*:147–150, 1974, with permission.)

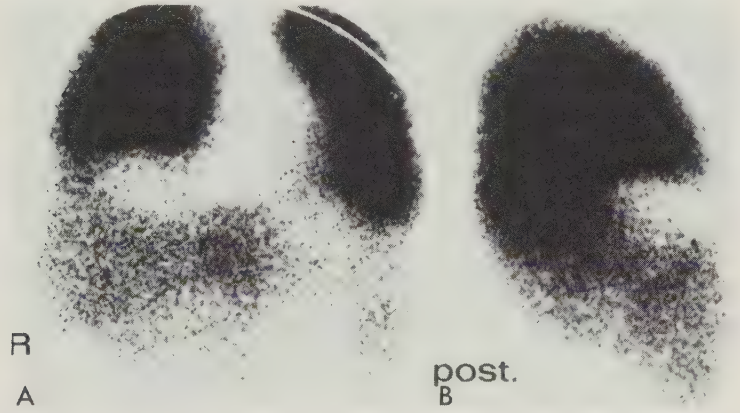

Figure 8. A 9 year old boy with a 5 week history of fever while on antibiotics was admitted with a large and tender liver. He had known chronic granulomatous disease since age 3. Fluoroscopy showed normal motion of diaphragm. Liver/lung scan shows separation of these organs. Surgery disclosed a 6 cm abscess in the right lobe, extending into the subphrenic space. (*From* Preimesburger, K., and Goldberg, M.: Radiology, *110*:147–150, 1974, with permission.)

steps to follow; if the patient is clinically stable, and the scan indicates a limited defect, management can be nonoperative[54] (Fig. 3). Multple view gamma camera liver imaging can be accomplished quickly and safely even in the critically ill or immobilized patient, who might not be able to undergo arteriography.[54, 67] The disadvantages of paracentesis in this situation are set out more fully below.

Radioactively labeled rose bengal can be used to generate two types of information in the diagnostic work-up of the jaundiced patient: The first is a numerical estimate of polygonal cell function, obtained by determining the rate of clearance of the drug from the blood and expressed as the ratio of the counts obtained at 20 minutes and 5 minutes (the 20/5 minute ratio).

The second type is a pictorial demonstration of the functioning status of the biliary tree.[50, 73] The addition of imaging information has

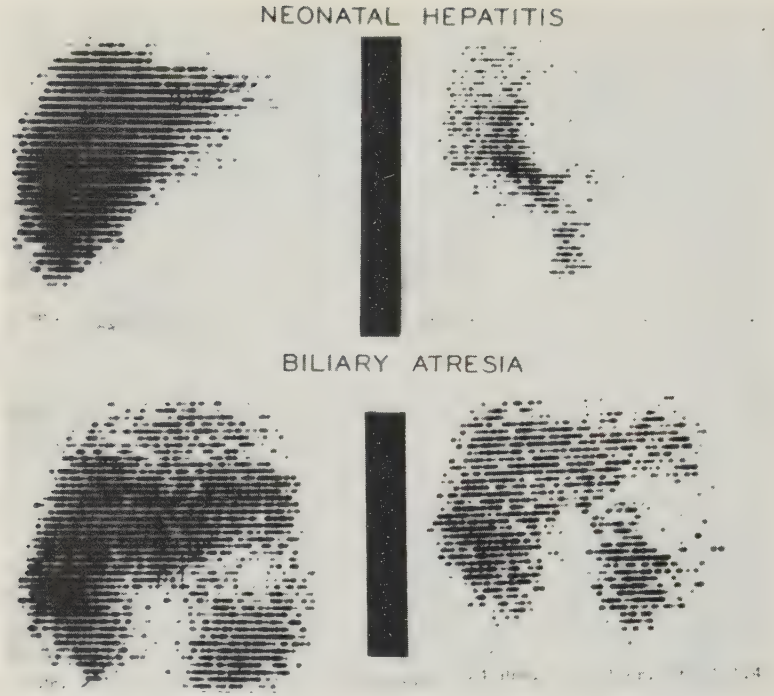

Figure 9. *A*, Rectilinear scan at 1 and 24 hours in an infant with neonatal hepatitis; excretion of I-131 rose bengal, though delayed, is evident by bowel radioactivity at 24 hours. A 72 hour stool collection (10 per cent) exceeds that found in biliary atresia. *B*, Comparable studies in an infant with biliary atresia. Extrahepatic activity is unchanging indicating that it is in the kidney, not the bowel. Minimal activity is recovered in the stool. (*From* Silverberg, M., et al.: Sem. Nucl. Med., 3:69–80, 1973, with permission.)

made the ^{131}I rose bengal study much more useful, especially in pediatric and neonatal problems (see below). Normally, the rose bengal will be seen in the gastrointestinal tract within 1 hour after injection. Intrahepatic disease can lead to varying degrees of cholestasis, but failure to see evidence of rose bengal excretion in 48 hours affords reliable evidence of a complete extrahepatic block even when the 20 to 5 minute ratio is greater than 90 per cent.[73] Imaging might show some passage of activity into the gut when a 20/5 minute ratio under 70 per cent suggests surgical jaundice. This apparent contradiction is probably the result of a ball valve type of obstruction and has been reported to occur in about 5 per cent of cases.[33]

The differential diagnosis of prolonged neonatal jaundice has always posed difficulty, particularly in distinguishing idiopathic neonatal hepatitis from biliary atresia. Stool counting for excreted ^{131}I rose bengal was initially suggested for indirect evidence of biliary tract patency.[14, 30] Fair success has been obtained,[62] especially with the use of oral cholestyramine to reduce the area of overlapping results.[53] Since the stool collection method has several technical disadvantages, abdominal imaging is being used to detect whether the ^{131}I rose bengal reaches the gastrointestinal tract (Fig. 9). This combined approach results in few, if

any, false-negative results. Intrahepatic cholestasis may be so severe, however, that it cannot be differentiated from biliary atresia even with this technique.[59]

PANCREAS

The pancreas deserves its reputation as the silent organ. It is inaccessible to palpation and it offers no easy access to conventional radiographic techniques. Vascular radiology and nuclear medicine have, in recent years, developed techniques which have reduced these difficulties to some extent. It is essential that the clinician clearly understand the type of information which may be obtained and the limits of certainty that can be reached by these methods. Most importantly, he must learn to distinguish those clinical conditions which can be evaluated by nuclear imaging.

Imaging of the pancreas can currently be performed with only one radiopharmaceutical, selenomethionine, an analog of the amino acid methionine, in which the sulfur atom has been replaced by a radioactive selenium atom (selenium-75). For several reasons, this preparation is less than satisfactory. First, selenomethionine is not specific for the pancreas. It is concentrated by the pancreas and liver in the course of enzyme and other protein synthesis. Because of the liver's greater mass, a much larger fraction of the administered dose is taken up in that organ. Visualization of the pancreas may then be obscured by an overlapping liver image (Fig. 10). Some have employed double isotope scanning using a liver-specific agent plus selenomethionine and various elec-

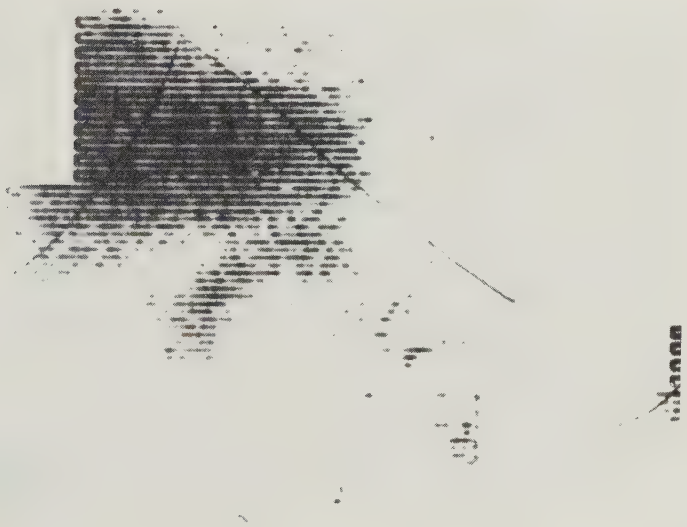

Figure 10. Normal pancreas scan illustrating the large percentage of activity in the liver; a small amount of radioactivity is present in the proximal small bowel. (*From* Bouchier, I. A. D., et al.: Clin. Gastroenterol., *1*:105–118, 1972.)

Table 2. *Extrapancreatic Causes of Abnormal Scans*

EXTRAPANCREATIC DISEASE
Peptic ulcer
Biliary tract disease
Liver disease (cirrhosis, hepatitis)
Carcinoma anywhere in the gastrointestinal tract
INTERRUPTION OF NORMAL PHYSIOLOGY
Nasogastric suction
Gastroenterostomy
Vagotomy/pyloroplasty
Too ill to eat, or starving

tronic image subtraction techniques to lessen this problem: mixed results have been reported.[2] The second disadvantage of selenomethionine is that selenium-75 has a long half life and emits medium energy gamma rays and beta particles.

The radiation dose which results from these physical decay characteristics limits the amount of the drug that can be given a patient. This limitation reduces the number of counts that can be accumulated in an image and hence the diagnostic reliability of the image. Nevertheless, in the proper clinical context, important useful information can be obtained by this study.

Those who have systematically reviewed and reported their experience with pancreatic imaging agree that the pancreas scan is a highly sensitive study but that it is quite nonspecific. In a summary of 13 reported series, the combined true-positive rate was over 90 per cent but the false-positive rate was over 30 per cent. It is the nonspecificity of the abnormal study that constitutes the major problem in pancreatic imaging. The study may be abnormal with pancreatic disease, including diabetes, in extrapancreatic disease, or with no disease at all. It is now accepted that diabetes and a number of nonpancreatic conditions (Table 2) have a high probability of causing an abnormal pancreas scan. It is likely that these patients have suffered disruption of the mechanisms which regulate the pancreatic function responsible for normal uptake and distribution of the selenomethionine.

The problem of the false-positive study can be reduced, then, by an aware selection of patients for pancreas imaging. In patients with the conditions listed in Table 2, imaging should not be considered a screening procedure. In these patients, no significance should be attributed to the study that is not unequivocally normal.

In a few reported series pancreatic scans and angiograms have been performed on the same patients.[34, 58] Overall, the addition of the angiogram has not appreciably improved diagnostic accuracy in these groups. These limited data suggest that (1) the scan and angiogram have roughly the same accuracy in detecting disease, and (2) when they are in conflict, one is as likely to be wrong as the other.

Despite the sensitivity reported for pancreas imaging, it is discouraging that the preoperative diagnosis of pancreatic tumor has had no effect on patient survival. Carcinoma involving the pancreas manifests symptoms relatively late so that even in "early" cases, the tumor is large. In one review, only one patient with primary pancreatic cancer was alive 12 months after diagnosis.[44] Of 57 tumors, 14 were resectable (5 periampullary, 5 lower duct, and 4 pancreatic).

Under these circumstances it would be reasonable to ask, "Why undertake radionuclide imaging of the pancreas?" The answer is that many more patients are suspected of having pancreatic disease than do, in fact, have it. For these people, pancreatic imaging may be a reliable test by which to exclude disease. In this large group of patients, a negative scan allows attention to be turned to the other diagnostic possibilities.

It is important to point out that it is not uniformly accepted that pancreas imaging has produced results which justify its use as a standard diagnostic study. This point of view has been presented in some detail by Bachrach et al.[9] who emphasize the nonspecificity of the abnormal scan, the difficulty caused by liver uptake and the general problem of image interpretation. There can be little doubt that the achievement of reliable results in radionuclide imaging of the pancreas requires technical excellence and experienced judgment on the part of the nuclear medicine physician. Without these, neither the clinician nor the patient can anticipate useful results from this study.

SPLEEN

Radionuclides can be used to good effect in a number of clinical problems involving the spleen. Those of major interest to us are (1) the differential diagnosis of left upper quadrant masses; (2) the evaluation of the patient with possible splenic trauma; (3) the detection of splenic mass lesions such as infarct, abscess, or tumor, or (4) the detection of ectopic or accessory splenic tissue; and (5) evaluation of the role played by the spleen in hemolysis.

Imaging of the spleen can be carried out by using either radioactive colloids as in liver imaging, or by using heat-treated (i.e., damaged) red blood cells. The latter are usually labeled with chromium 51-sodium chromate ($T^1/_2$, 27 days) although methods of labeling with technetium 99m pertechnetate have recently been developed.[23, 24] The latter radiopharmaceutical with its shorter physical half-life and absence of beta emission produces higher quality images with a lower radiation dose to the patient. While colloids are easier to use for imaging, damaged red cells are spleen specific and often must be used when accessory or ectopic splenic tissue is being sought. Red cell trapping by the spleen can be estimated by administering non–heat treated labeled red cells and counting over the spleen, liver and precordium at intervals for one to three weeks. The chromium-51 label is required for this study because of the time span involved.

Spleen imaging was not commonly undertaken when labeled red

cells or colloidal radiogold were the only radiopharmaceuticals available. However, the introduction of technetium sulfur colloid has afforded a simple, safe, rapid, and reliable method of evaluating size and gross morphology of the spleen. At the present time, radionuclide imaging together with the upper gastrointestinal tract examination is the first line of investigation in the patient who has a diagnostic problem in the left upper quadrant. Splenomegaly itself often cannot be determined with certainty on clinical grounds alone. The spleen scan can establish the actual size and location of the organ; when normal, it excludes the spleen as the site of pathology in the differential diagnosis of a left upper quadrant mass.

This progress in spleen imaging has had a significant effect on the diagnosis and treatment in the trauma patient. The spleen, like the liver, can be seriously damaged by penetrating and nonpenetrating trauma that ranges from severe to slight. At either end of this spectrum, damage to the spleen can be overlooked. Wilcox found the ratio of nonpenetrating to penetrating trauma as a cause of splenic rupture to be greater than 30 to 1.[72] In the severely injured patient, particularly the unconscious one, if splenic injury can be excluded, attention may be diverted to more obvious problems such as fractures and facial injuries.[51] In the acute case, Pratt et al. have recommended peritoneal tap when the diagnosis of spleen rupture is not obvious.[56] Diagnostic paracentesis has serious drawbacks. First, it can detect only an already ruptured organ, while scanning can detect intrasplenic or subcapsular hemorrhage prior to rupture. Second, a multiple-view gamma camera study can be done in as little or less time than four quadrant paracentesis at considerably less risk to the patient. In the non-acute case, the same authors have suggested that "expectant observation" be used for at least 7 days after trauma to the left side to guard against delayed splenic rupture.[56] However, in this group of patients, too, radionuclide imaging has been proven to be a reliable screening study. Diagnostic accuracy of both positive and negative studies has been 90 per cent or greater.[26, 42, 48]

Nebesar's group believes that imaging should be the initial procedure in the investigation of the patient with possible spleen trauma.[48] Based on their experience with angiography, they found (1) the scan is easier to perform and interpret; (2) it yields less equivocal results than angiography; and (3) if multiple organ injuries are suspected, radionuclide imaging of each one (e.g., liver, spleen, kidney) can be quickly accomplished. If one or more of these are equivocal, then the arteriogram should follow. Others suggest that if the spleen scan is completely negative, the angiogram might be omitted.[42]

Minor trauma may not raise the suspicion of splenic injury. Nevertheless, spleen imaging should be done even when an injury seems trivial. The diagnosis of splenic damage can be made before rupture in a greater number of patients if spleen imaging is more widely used. Prompt screening of patients with trauma to the left side will reduce the risk of missing delayed rupture in suspicious cases, and when negative the scan can eliminate unnecessarily prolonged hospitalization. In sum, the spleen should be scanned in anyone who (1) has had sufficient trauma to fracture a rib, (2) has left upper quadrant pain or guarding after slight trauma, or (3) has x-ray evidence of lung contusion.[52] Three

Figure 11. Oblique scintigram demonstrates splenic enlargement with a large filling defect along the inferior lateral margin; at surgery there was a long stellate laceration and clot in the corresponding area of the spleen. (*From* O'Mara, R., et al.: Surg. Gynec. Obstet., *131*:1077–1084, 1970, with permission.)

cases illustrating the characteristic findings in such patients are seen in Figures 11 through 13.

The abnormal spleen scan can also be caused by tumor,[31] abscess,[37,75] cyst, or infarct.[49,68] When any of these conditions enters the differential diagnosis, spleen imaging should be performed early. Splenic abscess, which occurs most often by hematogenous spread from the primary site of infection, has been diagnosed preoperatively by scanning in varied conditions. Three interesting examples are porcine gastroenteritis in a pig farmer, after lower extremity amputation in a diabetic patient, and after prostatic biopsy.[75]

Splenic function, rather than structure, is the basis for evaluating whether splenectomy will benefit the patient with refractory anemia. The role the spleen may play in producing premature red cell destruction is determined by counting over the spleen, liver, and precordium as described earlier. Over the same time period, the disappearance of the labeled cells from the circulation is measured to estimate the red cell survival. If the red cell count rate over the spleen reaches a level two to three times that in the blood or liver, a favorable response to splenectomy is likely. There are a number of reports in the literature detailing the technique and results.[3,66,69] Predictions have been accurate in 80 to 90 per cent of patients operated upon. False-positive studies have been uncommon. There have been a few patients with negative studies, i.e., no evidence of splenic sequestration, who have nevertheless responded to a splenectomy performed on clinical grounds. The reasons for this may be related to the difficulty in obtaining representative data from an enlarged, infiltrated, or infarcted organ.[66] In patients with myelofibrosis, prediction of the effect of splenectomy is particularly difficult.[66] The

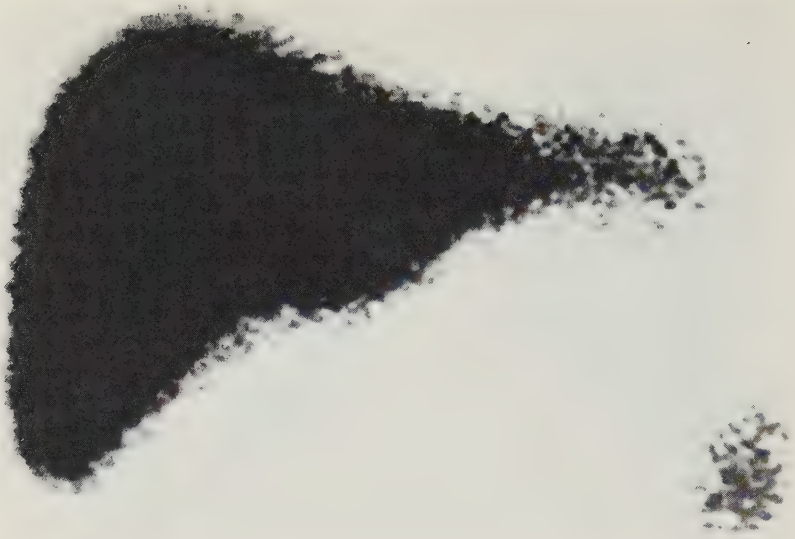

Figure 12. Anterior scintigram shows massive defect across the mid-portion of the spleen; surgery showed a laceration at this site. (*From* O'Mara, R., et al.: Surg. Gynec. Obstet., *131*:1077–1084, 1970, with permission.)

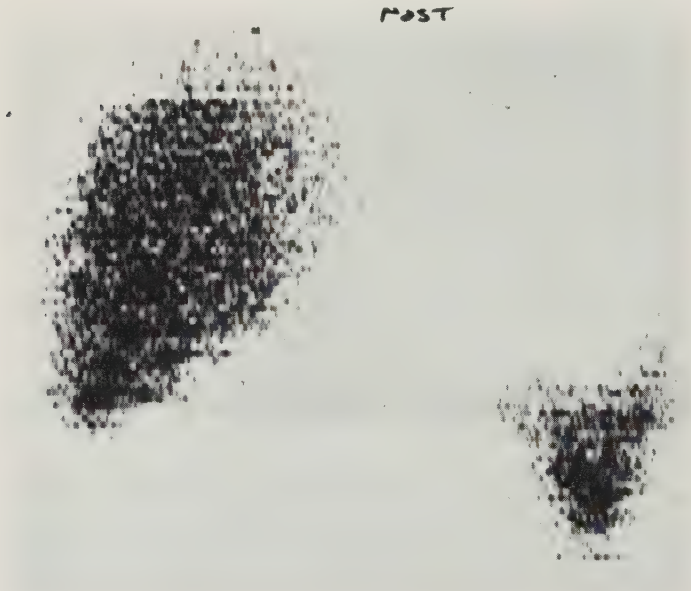

Figure 13. Posterior rectilinear scan (with the spleen oriented to the reader's right) in an 18-year old boy with a 1 week history of dysphagia; a barium swallow showed a left upper quadrant mass displacing the stomach to the right. The functioning lower pole of the spleen is displaced downward by a large nonfunctioning mass replacing the organ. At surgery, a large subcapsular and intrasplenic hematoma was disclosed.

organ may be massively enlarged and may be a site of extramedullary hematopoiesis. Nevertheless, if the patient's transfusion demands are too great, splenectomy may have to be considered when chromium-51 studies indicate a short survival half time and evidence of destruction of red cells in the spleen.

A similar approach to thrombocytopenic disorders has proven useful. The patient's spleen, liver and precordium can be counted after he has received chromium-51 tagged platelets. When the surface counting indicates splenic sequestration, patients have responded to splenectomy with an increase in their platelet count and no further need of medical therapy.[19]

CONCLUSION

The studies evaluated in this article do not exhaust the potential applications of nuclear medicine to clinical problems involving the liver, spleen, and pancreas. They are, however, those most widely used and tested by experience. This experience has been the result of developments in radioisotope production and radiopharmaceutical synthesis, of the introduction of new imaging equipment and computers, and of a general broadening of our knowledge about drug localization and pathophysiology. Advances in these areas are continuing and consequently further developments can be expected in our ability to contribute to the diagnosis and management of diseases of the liver, spleen, and pancreas.

The particular strengths of a nuclear medicine department will depend to a great extent on the experience and interests of the nuclear medicine staff. The clinician will best be able to exploit these strengths for his patients' advantage by maintaining close communication with his colleagues in nuclear medicine.

REFERENCES

1. Abbruzzese, A. A., and Nazir-Uddin, K.: Pyogenic abscess of the liver. Amer. J. Gastroenterol., 58:288–298, 1972.
2. Agnew, J. E., Youngs, G. R., and Bouchier, I. A. D.: Conventional and subtraction scanning of the pancreas: an assessment based on blind reporting. Brit. J. Radiol., *46*:83–98, 1973.
3. Ahiya, S., Lewis, S. M., and Szur, L.: Value of surface counting in predicting response to splenectomy in hemolytic anemia. J. Clin. Path., 25:467–472, 1972.
4. Ahsen, O., and Pickren, J.: The topographic distribution of liver metastases—its relation to surgical and isotope diagnosis. J. Nucl. Med., 3:149–152, 1962.
5. Altemeier, W. A., Schowengerdt, C. G., and Whitely, D. H.: Abscesses of the liver: surgical considerations. Arch. Surg., *101*:258–265, 1970.
6. Andrews, J. T., Cox, K. R., Hare, W. S. C., et al.: Liver scanning for the detection of metastases following colorectal cancer surgery. Austral. New Zeal. J. Surg., *43*:66–72, 1973.
7. Andrews, J. T., Steven, L. W., Arkles, L. B., et al.: Reticuloendothelial and blood pool scanning and the diagnosis and differentiation of space occupying lesions of the liver. Austral. New Zeal. J. Surg., *43*:14–18, 1973.
8. Ariel, I. M., and Molander, D.: Hepatic gamma scanning—an aid in determining treatment policies for carcinoma involving the liver. Amer. J. Surg., *118*:5–14, 1969.
9. Bachrach, W. H., Birsner, J. W., Izenstark, J. L., et al.: Pancreatic scanning: a review. Gastroenterology, *63*:890–910, 1972.
10. Bender, M., Blau, M., Bahski, S., et al.: Value of radioisotope scanning for detection of pancreatic tumors. Cancer Bull., *22*:113–115, 1970.
11. Berke, R. A., Saenger, E. L., and Bahr, G. K.: Decision making in nuclear medicine: 1. brain imaging. J. Nucl. Med., *14*:850–853, 1973.

12. Block, M. A., Schuman, B. M., Eyler, W. R., et al.: The liver photoscan in the recognition and management of abdominal masses. Henry Ford Hosp. Med. Bull., *14*:85–94, 1966.
13. Bouchier, I. A. D., Youngs, G. R., and Agnew, J. E.: Pancreatic scanning. Clin. Gastroenterol., *1*:105–118, 1972.
14. Brent, R. L., and Geppert, L. J.: The use of radioactive rose bengal in the evaluation of infantile jaundice. Amer. J. Dis. of Childh., *116*:257–261, 1968.
15. Briggs, R. C.: Combined liver-lung scanning in detecting subdiaphragmatic abscess. Sem. Nucl. Med., 2:150–156, 1972.
16. Brown, D. W.: Combined lung liver radioisotope scan in the diagnosis of subdiaphragmatic abscess. Amer. J. Surg., *109*:521–525, 1965.
17. Castagna, J., Benfield, J. R., Yamada, H., et al.: The reliability of liver scans and function tests in detecting metastases. Surg. Gynec. Obstet., *134*:463–466, 1972.
18. Conn, H. O., and Elkington, S. G.: Is hepatic scanning overrated? Gastroenterology, *54*:135–139, 1968.
19. Cooper, M. R., Hauser, K. S., Maynard, C. D., et al.: Platelet survival and sequestration patterns in thrombocytopenic disorders. Radiology, *102*:89–100, 1972.
20. Davies, R., Vernon, M., and Croft, D.: Liver scans and the detection of clinically unsuspected liver metastases. Lancet, *1*:279–280, 1974.
21. Drum, D. E., and Christacopoulos, J. S.: Hepatic scintigraphy in clinical decision making. J. Nucl. Med., *13*:908–915, 1972.
22. Eaton, S. B., Ferrucci, J. T., and Benedict, K. T., Jr.: A comprehensive evaluation of radiologic exploration of the pancreas. CRC Critical Reviews in Radiologic Sciences, *1*:165–205, 1970.
23. Eckelman, W., Richards, P., Atkins, H. L., et al.: Visualization of the human spleen with 99m Tc labeled red blood cells. J. Nucl. Med., *12*:310–311, 1971.
24. Eckelman, W., Richards, P., Hauser, W., et al.: Technetium-labeled red blood cells. J. Nucl. Med., *12*:22–24, 1971.
25. Espiritu, C. R., and Rolfs, H. E.: Diagnostic accuracy of pancreatic scanning. Amer. J. Dig. Dis., *17*:539–543, 1972.
26. Evans, G. W., Curtin, G., McCarthy, H. F., et al.: Scintigraphy in traumatic lesions of the liver and spleen. J.A.M.A., 222:665–667, 1972.
27. Ferrante, W. A., and Maxfield, W. S.: Comparison of the diagnostic accuracy of liver scans, liver function tests, and liver biopsies. Southern Med. J., *61*:1255–1263, 1968.
28. Ferrier, F. L., Hatcher, C. R., Achord, J. L., et al.: The value of liver scanning for detection of metastatic cancer. Amer. Surgeon, *35*:112–120, 1969.
29. Fink, D. W.: Scintiphotographic demonstration of rupture of an accessory spleen. J. Nucl. Med., *13*:333–334, 1972.
30. Ghadimi, H., and Sass-Kortsak, A.: Evaluation of the radioactive rose bengal test for the differential diagnosis of obstructive jaundice in infants. New Eng. J. Med., *265*:351–358, 1961.
31. Gould, H. R., Clemett, A. R., and Rossi, P.: Radiologic diagnosis of splenic metastasis. Amer. J. Roentgen., *109*:755–760, 1970.
32. Grant, R. N., Morgan, L. R., and Cohen, A.: Hepatic abscesses. Amer. J. Surg., *118*:15–20, 1969.
33. Greene, A. G., and Sadowsky, N. L.: A radiologic approach to the differential diagnosis of surgical and non-surgical jaundice. Amer. J. Roentgen., *116*:368–374, 1972.
34. Hatchette, J. B., Shiler, S. E., and Murison, P. J.: Scintiphotos of the pancreas: analysis of 134 studies. J. Nucl. Med., *13*:51–57, 1972.
35. Jackson, G. L., and Abright, D.: Splenic rupture. J.A.M.A., *204*:930–931, 1968.
36. Janinski, W. K., Malinowska, J., Makiewicz, H., et al.: A scintillation camera and 1600 channel analyzer for the diagnosis of metastatic cancer of the liver. IAEA Symposium on Medical Radioisotope Scintigraphy, 1968, pp. 507–516.
37. Lepage, J. R., Pratt, A. D., Jr., Miale, A., et al.: Diagnosis of splenic abscess by radionuclide scanning and selective arteriography (case report). J. Nucl. Med., *13*:331–332, 1972.
38. Liewendahl, K., and Kvist, G.: Evaluation of pancreas scanning. Acta Med. Scand., *188*:75–80, 1970.
39. Lomas, F., Dibos, P., and Wagner, H. N. Jr.: Increased specificity of liver scanning with the use of gallium-67 citrate. New Eng. J. Med., *286*:1323–1329, 1972.
40. Lubin, E., and Lewitus, Z.: Indium-113m labeled transferrin as a blood pool marker to aid in differential diagnosis of cold areas on colloid liver scan. Sem. Nucl. Med., 2:128–132, 1972.
41. Lusted, L.: Decision making studies in patient management. New Eng. J. Med., 284:416–424, 1971.
42. Lutzker, L., Koenigsberg, M., Meng, C., et al.: The role of radionuclide imaging in spleen trauma. Radiology, *110*:419–425, 1974.
43. Magnum, J., and Powell, M.: Liver scintiphotography as an index of liver abnormality. J. Nucl. Med., *14*:484–489, 1973.
44. McCarthy, D. M., Brown, P., Melmed, R. N., et al.: 75-Se selenomethionine scanning in the diagnosis of tumors of the pancreas and adjacent viscera: the use of the test and its impact on survival. Gut, *13*:75–87, 1972.

45. McCready, V. R., and Cottrall, M. F.: Combined pancreas and liver scanning using a double isotope technique. Brit. J. Radiol., *44*:870–877, 1971.
46. McCrot, J. J.: Rupture or laceration of the liver by nonpenetrating trauma. Radiology, *78*:49–57, 1962.
47. Miale, A., Rodriguez-Antunez, A., and Gill, W. Jr.: Pancreatic scanning after ten years. Sem. Nucl. Med., *2*:201–219, 1972.
48. Nebesar, R. A., Rabinov, K. R., and Potsaid, M. S.: Radionuclide imaging of the spleen in suspected splenic injury. Radiology, *110*:609–614, 1974.
49. Nelp, W. B., and Kuhn, I. N.: Splenic infarct diagnosed preoperatively by photoscanning. J.A.M.A., *197*:368–371, 1966.
50. Nordyke, R. A.: Metabolic and physiologic aspects of I-131 rose bengal in studying liver function. Sem. Nucl. Med., *2*:157–166, 1972.
51. O'Mara, R. E.: Scanning in abdominal trauma. Postgrad. Med., *53*:109–113, 1973.
52. O'Mara, R., Hall, R., and Dambroski, D.: Scintiscanning and diagnosis of rupture of the spleen. Surg. Gynec. Obstet., *131*:1077–1084, 1970.
53. Poley, J. R., Batia, M., Boon, D. J., et al.: The combination of I-131 rose bengal excretion test and oral cholestyramine identifies obstructed bile ducts. (Abstract.) Gastroenterology, *62*:794, 1972.
54. Popovsky, J., Wiener, S. N., Felder, P. A., et al.: Liver trauma: conservative management and the liver scan. Arch. Surg., *108*:184–186, 1974.
55. Potsaid, M.: Radionuclide pancreatography. *In* Eaton, S. B., and Ferrucci, J. T.: Radiology of the Pancreas and Duodenum. Philadelphia, W. B. Saunders Co., 1973.
56. Pratt, D. B., Andersen, R. C., and Hitchcock, C. R.: Splenic rupture—a review of 114 cases. Minn. Med., *54*:177–184, 1971.
57. Preimesberger, K., and Goldberg, M.: Acute liver abscess in chronic granulomatous disease of childhood. Radiology, *110*:147–150, 1974.
58. Rodriguez-Antunez, A., Alfidi, R., and Gill, W.: Pancreas scanning. CRC Critical Reviews in Radiologic Sciences, *1*:25–46, 1970.
59. Rosenthal, S., and Kaufman, S.: The liver scan in metastatic disease. Arch. Surg., *106*:656–659, 1973.
60. Satish, G. J., Jordan, L., Jahns, M. F., et al.: Liver scintigrams compared with alkaline phosphatase and BSP determinations in the detection of metastatic carcinoma. J. Nucl. Med., *12*:227–230, 1971.
61. Sauer, R., Fahrlander, H., and Fridrich, R.: Comparison of the accuracy of liver scans and peritoneoscopy in benign and malignant primary and metastatic tumors of the liver. Scand. J. Gastroenterol., *8*:389–394, 1973.
62. Sharp, H. L., Krivit, W., and Lowman, J. T.: The diagnosis of complete extrahepatic obstruction by rose bengal I-131. J. Pediat., *70*:46–53, 1967.
63. Silverberg, M., Rosenthal, L., and Freeman, L. M.: Rose bengal excretion studies as an aid in the differential diagnosis of neonatal jaundice. Sem. Nucl. Med., *3*:69–80, 1973.
64. Steven, L. W., Andrews, J. T., and Arkles, L. B.: Experience with radioisotope scanning of the pancreas. Med. J. Austral., *2*:867–873, 1972.
65. Suzuki, T., Matsumato, Y., Manabe, T., et al.: Serum alpha fetoprotein and gallium 67 citrate uptake in hepatoma. Amer. J. Roentgen., *120*:627–633, 1974.
66. Szur, L., and Smith, M. D.: Red cell production and destruction in myelosclerosis. Brit. J. Hematol., *7*:147–168, 1961.
67. Vadas, M., McLaughlan, A. F., and Morris, J. G.: Emergency evaluation of liver trauma using the gamma camera. Med. J. Austral., *1*:56–58, 1973.
68. Vagenakis, A. G., Abreau, C. M., and Braverman, L. E.: Splenic infarct diagnosed by photoscanning. J. Nucl. Med., *13*:563–564, 1972.
69. Veeger, W., Woldring, M. G., VanRood, J. J., et al.: The value of the determination of the site of red cell sequestration in hemolytic anemia as a prediction test for splenectomy. Acta Med. Scand., *171*:507–520, 1962.
70. Watson, A., and Torrance, H.: Liver scanning in surgical practice. Brit. J. Surg., *57*:405–408, 1970.
71. Waxman, A. D., Telfer, N., and Siemsen, J. K.: Dynamic imaging of the spleen. J. Nucl. Med., *14*:582–584, 1973.
72. Wilcox, G. L.: Non-penetrating injuries of the abdomen causing rupture of the spleen. Arch. Surg., *90*:498–502, 1965.
73. Winston, M., and Blahd, W.: I-131 rose bengal imaging techniques and the differential diagnosis of jaundiced patients. Sem. Nucl. Med., *2*:167–175, 1972.
74. Yeh, S., Shih, W., and Liang, J.: Intravenous radionuclide hepatography in the differential diagnosis of intrahepatic mass lesions. J. Nucl. Med., *14*:565–567, 1973.
75. Zook, E. G., Bolivar, J. C., and Epstein, L. T.: The value of scintiscans and the diagnosis of splenic abscess. Surg. Gynec. Obstet., *131*:1125–1129, 1970.

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Pediatric Splenectomy

Indications, Technique, Complications, and Mortality

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The spleen is an organ more commonly considered in the therapy of hematologic abnormalities than as a basic surgical problem. Therefore, the surgeon finds himself most often acting as consultant-technician in the carrying out of the hematologist's desires. In this role, the surgeon must have clear ideas as to the place of splenectomy in the treatment of hematologic disease, must be conversant with the end results that can be achieved, and, above all, must be aware of the immediate and long-term complications that can ensue. The assessment of the indications for surgery and the hematologic end results fall within the province of the pediatrician; the operative and postoperative problems fall to the surgeon, while the long-term results and complications from the removal of splenic tissue should be assessed by both.

This consideration of splenectomy in childhood will be approached by a brief description of the rationale for this mode of therapy, the technique employed in carrying it out, some of the complications that occur in the performance of a splenectomy, and, finally, consideration of the mortality that can be expected in the use of this modality. The basic concepts will derive from a consideration of the experience with splenectomy at the Children's Hospital of Pittsburgh over a 25 year period from 1949 through 1973. In addition, allusions to the literature will be employed to substantiate or amplify certain points.

INDICATIONS FOR SPLENECTOMY FOR SPECIFIC CURATIVE RESULTS

Congenital spherocytosis is the prime indication for a splenectomy in childhood. As the name implies, there is a strong familial incidence of this condition in which the shape and resistance of the red cells are such as to leave them prey to easy destruction. This leads to crises with a bilirubin increment correlating with the decline in hemoglobin and

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hematocrit. This diagnosis must be considered in any child with anemia, and a work-up carried out to verify or disprove it. Splenectomy is curative in this disease. It should be borne in mind that an appreciable number of children suffering from congenital spherocytosis will have associated cholelithiasis. Every child so labeled should have a preoperative cholecystogram and adequate examination of the biliary tract at surgery. In our own experience with 309 splenectomies, we have found congenital spherocytosis to be the single most common cause for removal of the organ.

The spleen was removed for the first time because of *trauma* and dates back for probably a hundred years. In a children's setting, trauma still is the indication for splenectomy in 15 to 20 per cent of cases. Such trauma is predominantly the result of the automobile and it is more common, therefore, in the summer months when children are out of school and playing in the streets where they come in contact with moving vehicles with alarming frequency. As an occupant of a car in a motor accident, the child sustains splenic trauma at all times of the year. In areas where snow is commonly present, sledding accidents account for a certain amount of trauma in the wintertime. When a child has sustained such trauma and is seen by a surgeon, an assessment of the abdomen is somewhat difficult because of the voluntary and involuntary muscle-guarding resulting from the injury. Unless the examination is completely normal, a paracentesis should be performed in at least both lower quadrants and perhaps the upper quadrants as well. The insertion of a plastic catheter through the paracentesis needle will allow lavage of the peritoneal cavity with 250 to 500 cc of normal saline in order to get an accurate assessment of the presence or absence of blood. Obviously, withdrawal of frank blood from the paracentesis needle would obviate the necessity for the insertion of the plastic catheter and lavage. Where available, selective arteriography of the splenic artery may be indicated in some cases. It has been our experience that those situations in which the findings would be positive are those in which the evidence from other sources points unmistakably to a ruptured spleen. Trauma was the second most common cause for splenectomy in our hospital.

Idiopathic thrombocytopenic purpura (ITP) ranks third among indications for splenectomy and, as with trauma, may sometimes cause an acute bleeding episode in which diagnosis and splenectomy are urgent. This is particularly true in those children who have central nervous system evidence of bleeding from their thrombocytopenia. The mortality under such circumstances is distressingly high, and splenectomy can be a life-saving procedure. More often, the situation is one in which excessive bleeding and bruising call attention to the fact that an abnormality of clotting function may be present. It is of interest that about three-quarters of all cases of idiopathic thrombocytopenic purpura are self-limited in their course, but the remaining one quarter progress from the acute to the chronic phase. Steroids affect the bone marrow and result in maturing of the megakaryocytes and getting them into the circulation to raise an otherwise low platelet count. Remission is to be expected in 50 to 75 per cent of steroid-treated cases, but, if a 6 to 12 week course of this drug does not produce a response, then operation may be indicated.

Again, the area into which hemorrhage may occur can be the prime indication for early surgical intervention with variable results.

Relatively little is known of the natural history of *acquired hemolytic anemia.* The prognostic benefit of splenectomy, therefore, is difficult to define. A child smitten with this entity usually is so labeled only after an extensive hematologic work-up. The hemolysis which takes place can be either acute or chronic. Steroids have been found to be of benefit in some cases of this complex problem but are less successful than in idiopathic thrombocytopenic purpura. Splenectomy should be performed only when other treatment fails, because the best figures indicate only a 50 per cent chance of success. It is a rational form of therapy in spite of this yield, because it is felt that the disease may be the result of an autoimmune process and the removal of the spleen will take away a source of antibody formation. It is likewise postulated that destruction of red cells takes place in the spleen, and splenectomy would therefore be of benefit.

In *hypersplenism,* that situation in which the presence of an enlarged spleen signals the possibility of abnormal destruction of specific blood elements singly or in combination, splenectomy is seldom employed simply because of an abnormal blood count. Several types of hypersplenism may benefit from splenectomy, although they are not as predictable as one would like. Splenectomy in sickle cell disease can be used when radioisotope tagging indicates that there is significant red cell destruction or sequestration in the spleen. Idiopathic neutropenia or pancytopenia are occasional indications for removal of the spleen when other methods of treatment fail. Probably the most controversial indications for splenectomy for hypersplenism are in the management of aplastic or hypoplastic anemia. Removal of the spleen has been performed when there seems to be a definite inhibitory effect on the bone marrow by the presence of the spleen. The prognosis in all of the hypersplenic states following splenectomy is uncertain, but the procedure should not be discarded entirely.

Thalassemia major presents two situations in which splenectomy may be indicated. The first of these is the simple mechanical factor of a large spleen with which it is difficult to live and where the risk of trauma is ever present. Secondly, the spleen in this disease seems to play an active role in red cell destruction and therefore increases the need for transfusion. For these two reasons, splenectomy should be considered in a certain number of patients suffering from this form of hemolytic anemia. Because of the hemolysis factor in the disease, it is also well to remember the risk of cholelithiasis is increased, and all children who are to undergo the removal of the spleen for thalassemia major should have preoperative gallbladder studies and palpation of the organ at the time of operation.

Under certain circumstances, removal of the spleen is required when the venous pressure in the portal system is elevated. Such *portal hypertension* is almost always limited to the extrahepatic type of venous obstruction. Treatment in portal hypertension is aimed primarily at reducing portal pressure by some type of portosystemic shunting procedure. However, it has been shown in some cases by arteriography that, if

Table 1. *Indications for Splenectomy*

	CHILDREN'S HOSPITAL OF PITTSBURGH (309 cases)	AMERICAN ACADEMY OF PEDIATRICS[3] (1413 cases)
Congenital spherocytosis	86 (27%)	395 (27%)
Idiopathic thrombocytopenic purpura	45 (14%)	265 (18%)
Trauma	55 (17%)	348 (24%)
Thalassemia	8 (2%)	45 (3%)
Portal hypertension	26 (8%)	137 (9%)
Hypersplenism	10 (3%)	30 (2%)
Incidental to other surgery	17 (5%)	59 (4%)
Acquired hemolytic anemia	9 (2%)	18 (1%)
Hypoplastic anemia	5 (1.5%)	21 (1%)
Miscellaneous	48 (15%)	95 (6%)

the splenic vein is the blocked vessel, splenectomy will often be curative. One other aspect of portal hypertension requires consideration of splenectomy; that is, if hypersplenism in itself is severe enough to produce clotting derangements through reduced platelets or reduced resistance to infection resulting from neutropenia. Depression of thrombocytes in an adolescent girl about to undergo menarche can result in a considerable loss of blood. Selective removal of the spleen under these circumstances is beneficial. The surgeon needs to weigh the loss of the splenic vein as a possible vessel for splenorenal shunt against the potential benefit to be gained by splenectomy.

It is of interest to note in Table 1 the indications for splenectomy employed in our own experience and in the large collected series reported by Eraklis et al.[3]

TECHNIQUE

Under ordinary circumstances, splenectomy is a straightforward, clean, and uncomplicated operation, especially if the size of the organ is not greatly increased. Careful preoperative evaluation and preparation enhance the safe conduct of the procedure. Unless one has a critical situation in which bleeding is endangering the life of the child, one should never undertake the removal of the spleen at the time of any hemolytic crisis; operation during a period of remission is much more desirable.

Routine blood work-up should be done to assure that the patient has an adequate hemoglobin and hematocrit. If the count is low, it is often advisable to administer packed cells rather than whole blood. In those situations in which thrombocytopenia is present, there is a division of opinion as to the time that one should administer exogenous platelets. The effective life of platelets is such that, to make them maximally effective, they should be given as near to (or during) the operation as possible. There are those who like to have them given the night before, but an equal group would prefer to withhold them until the start of the operation. Our own particular preference is to administer the platelets

the night before and have freshly drawn blood with its active platelet component available at the time of surgery.

The administration of blood or any of its components is, of course, dependent upon there being an adequate, large gauge, intravenous line in the child. The method by which this line is introduced depends upon the age of the child and the availability of veins. One should be certain that there is a good means of introducing the proper blood elements if they are needed.

Individual surgeons have their preference as to the body position and incision location for the performance of the splenectomy. For many years we have used the standard left subcostal incision in children who have had that side slightly elevated so as to enable one to go out into the left flank. We have used a vertical paramedian or left rectus incision on a few occasions when the size of the spleen would dictate a larger opening than that provided by the subcostal incision. Our skin incision is generally made from the mid left rectus muscle lateralward, using the electrodissector to reduce the amount of bleeding encountered. The left rectus fascia is incised with a cold scalpel because we have hesitated to devitalize the fascia with a Bovie; on occasion we have had evisceration of abdominal incisions that led us to believe that fascial devitalization by cautery allowed for sutures to pull out. The left rectus muscle is actually retracted medialward without dividing it, unless the size of the spleen dictates that one needs the full length of the incision. The external and internal obliques and transversus muscles are transected to enter the abdominal cavity. Again, we do not open the peritoneum with a Bovie for the same reason as stated above regarding the rectus fascia.

The great hazard of a splenectomy is uncontrollable bleeding in a situation in which one does not have adequate access to the bleeding point. For this reason, in children generous mobilization of the spleen is practiced. We have preferred to be able to bring the spleen up onto the abdominal wall when possible. Some people have advocated the necessity for isolating the splenic artery and vein along the superior border of the pancreas as the first step in splenectomy as a means of control of major hemorrhage, should it occur during removal of the spleen. We have not felt that this was necessary and have seldom used it but do believe that the spleen should be freed from its avascular attachments to the diaphragm, colon, and kidney before one approaches the hilum. At times, splenitis which has occurred from the hematologic abnormality makes removal of the spleen from the under side of the diaphragm a somewhat bloody procedure; however, this is the exception rather than the rule.

The next step in the procedure is to release the superior pole of the spleen from the vasa breva attachment to the stomach. Sometimes these vessels are quite short and one must secure them carefully. Having mobilized the spleen fully, we have found it helpful to pack the subphrenic space with a Kurlex roll and to elevate the spleen on this roll so that it does not drop into the depths of the incision. The hilum is now approached, and, in children, this is seldom a fatty, difficult area in which to work. Vessels should be doubly clamped and divided individually wherever possible. This is particularly true at the superior and

inferior poles of the spleen before the major vessels are approached. Each vessel encountered should be tied and then suture-ligated on its proximal side to eliminate the hazard of postoperative hemorrhage.

As one approaches the hilum to get the major artery and vein, it should be done centrally so as to reduce the inadvertent opening of some of the branches of these vessels after they have left their single main source. It is an old dictum, but one to which we adhere whenever possible, that the artery should be identified and ligated before the vein is approached. This prevents the spleen from filling up and taking a certain amount of the circulating blood volume away from the child. We also believe that a degree of auto-transfusion can be carried out by squeezing the spleen after the artery has been tied and suture-ligated. Some feel that the introduction of a small dose of 1:1000 epinephrine can aid in this endeavor. Finally, the vein is secured and the specimen removed.

There are several points of operative caution in splenectomy. The anatomic variance of the position of the tail of the pancreas in relation to the hilum of the spleen is such that it must be carefully observed and dissected away so as not to produce traumatic pancreatitis or pancreatic injury with subsequent fistula or pseudocyst formation. Having removed the spleen, there are two things that should be done to adequately complete the procedure. First, a thorough search must be made for accessory spleens. Accessory splenic tissue has been found in approximately one quarter of our patients. The four common sites for extra splenic tissue are the hilum of the spleen, the tail of the pancreas, the gastrosplenic ligament, and the greater omentum. The hilum of the spleen is the predominant area in which accessory spleen(s) are found. It is incumbent upon the surgeon to be as atraumatic as possible in splenectomy, since lymph nodes and fat that have blood in them may resemble accessory spleens grossly. When in doubt, it is better to remove these pieces of tissue, because expected good results from removal of the major spleen may be compromised by leaving accessory tissue. Accessory spleens will hypertrophy and become a functioning unit that assumes the role of the removed spleen.

Secondly, as noted above, some of the hemolytic problems for which splenectomy is performed predispose the patient to cholelithiasis. Careful palpation of the gallbladder and biliary tree is the minimum surgical effort that should be employed in those patients in whom cholelithiasis was found on the preoperative cholecystogram. If one palpates stones in the gallbladder, an extension of the incision will be necessary to perform a cholecystectomy. There are, of course, situations in which one should not add a cholecystectomy to a difficult splenectomy in an acutely ill child. However, it is generally agreed that removal of the gallbladder should be accomplished at the primary procedure when possible.

There is a difference of opinion among surgeons as to whether, in the closure of the splenectomy incision, drainage should be instituted. It is the author's opinion that hemostasis should be achieved to a degree that assures no oozing or bleeding vessels, and most of our splenectomies are closed without drainage. We believe that drains are a source of ingress for bacteria, as well as egress for blood and lymph. This is a

valid reason for not draining the subphrenic bed. If, for any reason, there is uncertainty about the vessels or the tail of the pancreas, we do not hesitate to insert a stab-wound drain for a couple of days. This is, in fact, an indicator drain, not a therapeutic drain.

COMPLICATIONS

The complications encountered in our own experience and in the larger American Academy of Pediatrics Surgical Section Survey[3] are listed in Table 2.

Evisceration

This dreaded complication is not peculiar to pediatric patients undergoing splenectomy but did occur in the series from our hospital in 2 patients,[5] giving a 1 per cent incidence. It has been reported by others to be more frequent, but accurate approximation of all layers from the peritoneum outward should prevent the occurrence, because the child is healthy from a nutritional and metabolic standpoint in most cases. This, of course, is not the case in those splenectomies done for malignant disease, and the incidence of wound weakness might be expected to be higher under those circumstances.

Hemorrhage

Abnormal blood loss associated with splenectomy can occur at two times—during the procedure and in the first 24 to 48 hours after removal of the spleen. Operative hemorrhage is usually the result of the inadvertent tearing of one of the hilar vessels and is particularly difficult to control in an obese patient who has an excess of adipose tissue in the hilar region. Occasionally, hemorrhage will occur from the vasa breva of the stomach. The secret in controlling this type of hemorrhage is prevention by the adequate visualization of the vessels to be divided and tied. Postoperative hemorrhage usually occurs from inadequate hemostasis at the time of operation with the subsequent slippage of a ligature. This is an unusual occurrence and can be obviated by a tie and distal suture ligature technique. The avoidance of mass ligature tech-

Table 2. *Postoperative Complications of Splenectomy*

	CHILDREN'S HOSPITAL OF PITTSBURGH[5] (205 cases)	AMERICAN ACADEMY OF PEDIATRICS[3] (1413 cases)
Incisional	2 (1%)	47 (3.3%)
Hemorrhage	0	42 (3.0%)
Infection (nonfatal)	5 (2.5%)	–
Infection (fatal)	1 (0.5%)	–
Pancreatitis	0	25 (1.7%)
Others	5 (2.5%)	64 (4.5%)
	13 (6.3%)	178 (12.6%)

nique in the hilum is also a good prophylactic measure to eliminate postoperative bleeding. In a collected series of 1413 patients reported by Eraklis and Filler,[3] there were 42 cases of postoperative bleeding complications, an incidence of 3 per cent.

Infection

While splenectomies have been done since the dawn of surgery, it was an article by King and Shumaker[6] in 1952 that focused attention upon the possible increased association of infection in the post-splenectomy state in children. Careful observations made on a small group of 5 patients suffering from congenital spherocytosis who all suffered bouts of overwhelming sepsis, from which 2 succumbed, led the authors to some interesting suggestions as to the interrelationship of asplenia and infection. They made four observations: (1) splenomegaly occurs in the presence of many types of infection; (2) many latent infections are reactivated following splenectomy; (3) there is some suggestive evidence that, in certain animal species, splenectomy depresses the natural resistance to acute and chronic infections; (4) since the spleen is the largest single reservoir of lymphocytes in the body, and since the lymphocytes have been demonstrated to have a major role in antibody formation, the spleen would appear to play a leading part in this important defense function.

Since this significant paper, many authors have investigated the interrelationship of splenectomy in childhood and serious infection. Three reports in the last 7 years seem important enough to review briefly. A series of 467 patients from the Children's Hospital Medical Center in Boston were reviewed with extensive follow-up.[2] The average period of observation was over 6 years, and only proven bacteremia and bacterial meningitis were considered to be overwhelming infections. Over 5 per cent of the children showed overwhelming sepsis by this definition. Those conditions leading to splenectomy which carried the highest incidence of overwhelming infection were (from the highest to the lowest): thalassemia major, histiocytosis and inborn errors of metabolism, portal hypertension, cancer with splenomegaly, and idiopathic thrombocytopenic purpura. These carried at least a 5 per cent mortality from overwhelming infection. It is of significance to note that in 55 patients who had splenectomies for trauma or incidental to other surgical procedures, there were no infections. Forty-two per cent of the total series were children under 4 years of age, and the incidence of death from infection was 8.1 per cent in this group. The interval between splenectomy and fatal infection showed that slightly over 80 per cent of the fatal infections occurred within 4 years.

The infection and mortality figures derived from the Boston series must be compared with the expected infection-mortality incidence in the population at large. A fine article bearing on this aspect of the problem, as well as the whole post-splenectomy sepsis picture, was recently written by Singer.[7] His data suggest the following: (1) In infants less than one year of age, mortality due to infection occurs in 0.3 per cent. (2) In children aged 1 to 7 years, the incidence of mortality due to infection is 0.07 per cent. (3) In children aged 7 to 14 years, the in-

cidence of fatal infection is 0.02 per cent. With these figures in mind, it is obvious that the mortality from infection as reported from Boston is markedly above that to be anticipated in the population at large.

Singer collected a series of 2795 patients from 23 reports in the literature in which accurate information and follow-up were available regarding infection in the post-splenectomy state. The results of this study are summarized in Table 3. The overall incidence of infection was 4.25 per cent and the mortality was 2.52 per cent. As found in the Boston series, the susceptibility to infection varied with the basic underlying disease, but the mortality associated with sepsis in asplenic persons is at least 200 times as frequent as in the population at large. Septic disease, when it does occur, is severe and rapidly progressive, and has a greater than 50 per cent chance of causing death. The author of this article points out that congenital asplenic patients are also at greater risk from infection. Ivemark[4] reported that 4 of 11 patients with congenital agenesis of the spleen and without associated anomalies developed meningitis (36 per cent). Meningitis developed in 5 (7.5 per cent) of 66 patients with congenital asplenia and congenital heart disease. Singer further suggests that children who have their spleens removed under the age of 2 are at much greater risk to overwhelming infection than are those undergoing splenectomy after that age. He says: "The incidence of infection in asplenic infants is almost 100 times as great as in infants with intact spleens." Finally, he noted in his review of the 2795 patients that the average time interval between splenectomy and the onset of sepsis was 4 years, but the range was from 13 days to 14 years.

A recent report by Constantopoulos[1] suggests that a substance found in splenic tissue, which he terms "tuftsin," may play a leading role in the defense against bacterial invasion. This substance is directly active upon white blood cells to stimulate phagocytosis. The number of active phagocytic cells may be reduced by 50 per cent in asplenic patients. This is an interesting new development which lends experimental support to the clinical observation that asplenic patients are more liable to overwhelming infection.

Systemic infection in the splenectomy series in our institution would seem to corroborate an increased vulnerability to sepsis in splen-

Table 3. *Postsplenectomy Infection, Incidence and Mortality*[7]

	TOTAL PATIENTS	SEPSIS INCIDENCE	SEPSIS MORTALITY
Trauma	688	10 (1.45%)	4 (0.58%)
Incidental splenectomy	233	5 (2.1%)	2 (0.86%)
Idiopathic thrombocytopenic purpura	489	10 (2.05%)	7 (1.43%)
Congenital spherocytosis	850	30 (3.52%)	19 (2.23%)
Acquired hemolytic anemia	67	5 (7.5%)	2 (2.90%)
Portal hypertension	221	18 (8.2%)	13 (5.90%)
Primary anemia	70	6 (8.5%)	5 (7.01%)
Reticuloendotheliosis	69	8 (11.5%)	7 (10.1%)
Thalassemia	109	27 (24.8%)	12 (11.0%)
	2795	119 (4.25%)	71 (2.52%)

ectomized patients.[5] Seven per cent of patients subjected to splenectomy had a serious infection, with half of them showing substantiated septicemia and one fourth dying. This serious infection rate is at least 100 times the expected rate in the general pediatric population. A corresponding increase in mortality rate is likewise present.

Because of the tendency to infection in patients who have undergone splenectomy, it has been felt by many that prophylactic treatment with antibiotics suggested by Smith[8] a decade ago should be given. In our own institution, this involves the administration of 200,000 units of penicillin twice a day by mouth for 2 years or until the child reaches the age of 5, whichever occurs later. In children under 2 years of age, consideration should be given to the possibility of administration of gamma globulin every 6 weeks to 3 months until the child reaches the age of 2 years.

Hyperthrombocytosis

There is often a rebound phenomenon following splenectomy in a child with depressed bone marrow. The danger of hypercoagulability has been emphasized by a number of authors, but in our experience has not been a problem. A tendency to greater clotting is judged by elevated platelet counts or clinical evidence of thromboembolic disease. For a number of years it has been our routine to obtain platelet counts every second or third day until discharge from the hospital. There is a precipitous rise in platelets after splenectomy, particularly when that splenectomy was done for hypersplenism or idiopathic thrombocytopenia. We have had a long-standing rule of thumb that children who showed greater than 1,000,000 platelets in the postoperative period probably should have anticoagulants administered. While a very occasional child has exceeded that limit, we have never administered anticoagulants for this reason. Our total experience with thromboembolic disease, for whatever cause, consists of less than 10 patients over a 25 year period, and none of these has been in conjunction with the performance of a splenectomy.

The large collected series[3] showed that only 7 of 1413 children received anticoagulants postoperatively. There was no report of thromboembolic disease in any patient.

Cholelithiasis

As suggested above, those hematologic conditions in which hemolysis of the red cells is the basic problem may result in hyperbilirubinemia and sedimentation with formation of biliary tract stones. We have made a preliminary study of the situation in regard to our 309 splenectomy patients. A total of 122 splenectomies were done for hemolytic disease. The various forms of red cell destruction encountered are listed in Table 4, along with those patients who showed cholelithiasis. Twelve patients proved to have cholelithiasis at the time of operation or in follow-up. They were equally divided between those who had stones palpated at the time of splenectomy and those who had cholelithiasis later in life. This 10 per cent incidence of gallbladder disease is a minimum figure because not all gallbladders were palpated at operation and only 50 per

Table 4. *Hemolytic Disease, Splenectomy, and Cholelithiasis*

		CHOLELITHIASIS
Congenital Spherocytosis	86	9
Acquired Hemolytic Anemia	9	1
Thalassemia Major	8	0
Sicklemia	4	2
Hypoplastic Anemia	5	0
Hypersplenism	10	0
	122	12

cent of the follow-up questionnaires were returned. The valid points to be made are: (1) all children in whom operation is contemplated for hemolytic disease should have preoperative cholecystograms; (2) all gallbladders in patients undergoing splenectomy for hemolytic disease should be palpated; (3) long-term follow-up of such patients indicates continuing vulnerability to cholelithiasis, even though the offending spleen has been removed.

Finally, it is of interest to note that most surgeons feel a cholecystectomy should be done with the splenectomy when stones are found. This assumes that there is no contraindication to its coincidental performance. In the 6 patients in our experience in whom stones were found at the table, 4 had cholecystectomy and the other 2 had the stones removed and the gallbladder left in; to date, no subsequent problems have ensued in the retained gallbladders.

MORTALITY

In Table 5 are recorded the mortality figures of our own experience, as well as those from the larger American Academy of Pediatrics Survey.[3] It is apparent that our mortality is over three times that of the survey; this can best be explained by the broader indications for splenectomy employed at our institution.

Among those children succumbing in the hospital were 8 patients suffering from extensive multiple trauma and those in whom splenec-

Table 5. *Mortality*

	CHILDREN'S HOSPITAL OF PITTSBURGH (309 patients)	AMERICAN ACADEMY OF PEDIATRICS[3] (1413 patients)
I. Unrelated to Hematologic Disease	15 (4.7%)	10 (0.7%)
Hospital 8		
Long-term 7		
II. Due to Primary Disease	21 (7.0%)	37 (2.6%)
Hospital 7		
Long-term 14		
	36 (11.7%)	47 (3.3%)

tomy was done incidental to correction of serious congenital anomalies. In addition, 7 patients died in the hospital of primary hematologic diseases, e.g., lymphoma, leukemia, reticuloendotheliosis, and portal hypertension. The 7 late deaths from nonhematologic diseases included metastatic carcinoma, neuroblastoma, hydrocephalus, Wilson's disease, adrenal hemorrhage, and an auto accident. Hodgkin's disease, leukemia, hypoplastic or aplastic anemia, and other lethal hematologic processes were not improved by splenectomy and led to deferred deaths in 14 patients.

REFERENCES

1. Constantopoulos, A., Najjar, V. A., and Smith, J. W.: Tuftsin deficiency: A new syndrome with defective phagocytosis. J. Pediat., *80*:564, 1972.
2. Eraklis, A. J., Kevy, S. V., Diamond, L. K., et al.: Hazard of overwhelming infection after splenectomy in childhood. New Eng. J. Med., *276*:1225, 1967.
3. Eraklis, A. J., and Filler, R. M.: Splenectomy in childhood: A review of 1413 cases. J. Pediat. Surg., *7*:382, 1972.
4. Ivemark, B. I.: Implications of agenesis of the spleen on conotruncus anomalies in childhood. Acta Paediat. Scand., *104*:1, 1955.
5. Kiesewetter, W. B., and Patrick, D. B.: Childhood splenectomy: Indications for and results from. Amer. Surg., *37*:135, 1971.
6. King, H., and Schumacher, H. B.: Splenic studies: Susceptibility to infection after splenectomy performed in infancy. Ann. Surg., *136*:239, 1952.
7. Singer, D. B.: Postsplenectomy sepsis. *In* Perspectives in Pediatric Pathology. Chicago, Illinois, Year Book Medical Publishers, 1973, pp. 285–311.
8. Smith, C. H., Erlandson, M. D., Stern, G., et al.: Post-splenectomy infection in Cooley's anemia: An appraisal of the problem in this and other blood disorders with consideration of prophylaxis. New Eng. J. Med., *266*:737, 1962.

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Current Management of Esophageal Varices

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Successful management of the patient with bleeding esophageal varices may tax and frustrate the most skilled clinician. Despite impressive progress in the understanding of the etiology, pathophysiology, and natural history of portal hypertension, the mortality remains high. Treatment is still largely directed toward palliating the sequelae without improving (and occasionally worsening) the underlying disease process. Frequent failure has bred a profusion of clinical approaches resulting in confusion and controversy. But order is emerging through new solutions and techniques—the benefit of accumulated experience and well controlled clinical trials.

This review will focus on two aspects of the problem. First, in the individual with active upper gastrointestinal bleeding, are varices present and are they the source of bleeding? Second, when varices are identified as a source of bleeding, what are the treatment options open to the surgeon?

A basic understanding of the pathophysiology of portal hypertension is necessary to evaluate the diverse therapeutic approaches in vogue today. Several recent monographs have examined, in thorough and colorful detail, this background and the current dilemmas.[3, 10, 11]

PATHOPHYSIOLOGY

The normal resting portal pressure varies between 5 and 15 cm of saline and no significant collateral flow exists between the portal and systemic venous circulations. As anatomic or physiologic obstruction (resistance) to portal flow develops, portal pressure rises. Increased splanchnic arterial inflow resulting from decreased arterial resistance and enlargement of the splanchnic bed contributes partly to the venous pressure rise. This increased "forward pressure" may partially explain

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why portal pressure often does not equilibrate to systemic venous pressure immediately after creation of a major portasystemic shunt.

As portal hypertension develops, collateral channels open and the increased flow escapes through multiple beds, such as those in the anterior abdominal wall and the retroperitoneum. The collaterals and, ultimately, the varicosities which form through the submucosal venous plexus in the upper stomach and lower esophagus and drain into the azygos system are, clinically, the most important because of the propensity of these varicosities to rupture with free bleeding into the upper gastrointestinal tract. As portal pressure rises above 25 to 30 cm of saline (occasionally reaching 55 cm), esophageal varices, hypersplenism, ascites, and hepatic encephalopathy are all frequent secondary effects. Bleeding from esophageal varices is unusual until portal pressure exceeds 25 or 30 cm of saline and direct measurement of portal pressure below that level virtually excludes bleeding varices as a source of upper gastrointestinal hemorrhage. Portal pressure may be determined directly by umbilical vein catheterization or at laparotomy by catheterization of the portal vein. Indirectly, reasonably accurate portal pressure can be determined by percutaneously measuring splenic pulp pressure in the unanesthetized patient. In the patient with cirrhosis, the hepatic vein wedge pressure is an accurate measurement of portal pressure.

ETIOLOGY

It is important to ascertain the location and cause of portal obstruction since optimal management is predicated on precise identification of pathology. Sherlock[20] has defined two major groups of obstruction based on combined anatomic and physiologic criteria. The first are those obstructions which are clearly presinusoidal and may be either extrahepatic or intrahepatic in location. The second major group are the intrahepatic cirrhoses where the block is not purely sinusoidal and that designation (sinusoidal) is discarded. Two far less frequently occurring categories are primary portal hypertension and the hepatic venous outflow obstructions (postsinusoidal). These categories are listed in Table 1.

Primary or idiopathic portal hypertension is a rare physiologic obstruction which may be initially intermittent with no obvious anatomic obstruction.[12] Later, narrowing of the more distal portal branches may be noted by contrast studies and sclerosis may be seen microscopically. Extrahepatic obstruction of the portal vein may be the result of portal vein thrombosis, either in early childhood or in adult life, secondary to sepsis, coagulopathy, or local compression by tumor. The intrahepatic causes of purely presinusoidal nature are schistosomiasis (which on a world-wide basis may be the most frequent cause of portal hypertension), myeloproliferative disorders, such as myelosclerosis or Hodgkin's disease, sarcoidosis, arsenic toxicity, congenital hepatic fibrosis, or primary biliary cirrhosis. The intrahepatic obstructions associated with the nodular cirrhoses (Laennec's or post-necrotic cirrhosis) are by far the most common cause in this country in the adult population. Hepatic

Table 1. *Etiology of Portal Hypertension*

PRIMARY (IDIOPATHIC) PORTAL HYPERTENSION
PRESINUSOIDAL
Extrahepatic
Portal vein thrombosis or obstruction (cavernous transformation)
Infection
Coagulopathy
Tumor
Splenic arteriovenous fistula
Hepatic artery–portal vein fistula
Splenic vein obstruction or thrombosis
Pancreatitis
Intrahepatic
Schistosomiasis
Myeloproliferative disorders
Hodgkin's disease, myelofibrosis, etc.
Sarcoidosis
Congenital hepatic fibrosis
Arsenic toxicity
Primary biliary cirrhosis
INTRAHEPATIC
Cirrhosis
Laennec's cirrhosis
Post-necrotic cirrhosis
HEPATIC VENOUS OBSTRUCTION
Budd-Chiari syndrome
Constrictive pericarditis
Congestive heart failure
Web of vena cava
Venocclusive disease

vein obstruction may be physiologic on the basis of constrictive pericarditis or right-sided heart failure or true anatomic venous obstruction, such as the Budd-Chiari syndrome, veno-occlusive disease, or webs of the vena cava.

The etiology can generally be established when the findings of portal vein pressure (PVP), hepatic vein wedge pressure (HVWP), portal venography, and liver histology are known. Extrahepatic portal vein obstruction is diagnosed on the basis of portal vein occlusion demonstrated by venography with normal HVWP and normal liver histology. The intrahepatic presinusoidal group is characterized by patency of the portal vein with elevated PVP but normal HVWP and appropriate changes in liver histology. The intrahepatic cirrhoses are distinguished by typical periportal changes, microscopically, with an HVWP that approximates PVP and generally a patent portal vein. Portal vein thrombosis may be seen, however, secondary to cirrhosis as stagnation of portal blood flow occurs. Hepatic venous outflow obstruction is infrequent but may be suspected by findings on venography and the inability to measure HVWP. Rare cases of splenic vein thrombosis with bleeding esophageal varices have been reported following pancreatitis or neo-

natal umbilical vein catheterization without the full-blown picture of portal hypertension.[23]

DIAGNOSIS

In the patient who has never had an upper gastrointestinal hemorrhage, esophageal varices may be discovered during evaluation of unrelated complaints or may be detected during the assessment of known liver disease. If varices are unexpectedly found by esophagoscopy or barium contrast study, a thorough investigation of liver function and histology should be undertaken with the aim of pinpointing the etiology of the portal hypertension. Varices may exist in the absence of overt physical evidence of advanced liver disease and this is especially true in prehepatic obstruction. If esophageal varices have never bled, they require no treatment other than general medical management of the portal hypertension and its underlying etiology. Long-term follow-up of patients with known varices has established that the majority will never experience an upper gastrointestinal tract hemorrhage. What triggers variceal rupture is unclear. A sudden transient rise in portal pressure may occur during vomiting or a Valsalva maneuver. Low-grade peptic esophagitis may predispose the individual to rupture of the varices, although frank esophagitis is clearly not a necessary precursor. The size of the varices and the degree of portal pressure elevation are not well-correlated with the probability of rupture.

In the actively bleeding patient, diagnosis and treatment must progress simultaneously. If varices are found, it must be determined that they are the source of bleeding, since approximately 25 per cent of patients with known esophageal varices who develop upper gastrointestinal hemorrhage will be found to be bleeding from nonvariceal sites, most notably from gastritis or peptic ulcer disease. In the patient with active upper gastrointestinal bleeding in whom varices are suspected, we prefer the following sequence of diagnostic studies.

Endoscopy

Direct inspection of the upper gastrointestinal tract by fiberoptic endoscopy has been an increasingly preferred initial step in the evaluation of acute upper gastrointestinal hemorrhage. In the hands of experienced endoscopists, accurate diagnosis of the bleeding site is made in 90 to 95 per cent of patients when endoscopy is performed within the first 24 to 48 hours following onset of bleeding. If endoscopy is delayed, the success rate drops precipitously because of rapid healing of many small mucosal lesions such as Mallory-Weiss tears, superficial gastritis, or shallow gastric ulcers.[5] Endoscopy has two distinct advantages to recommend it as an initial study. First, the direct identification of a bleeding site greatly simplifies the diagnostic process and endoscopy is an extremely low-risk procedure. Second, since over one third of all patients with an acute upper gastrointestinal hemorrhage will be found to have more than one abnormality, endoscopy provides direct evidence as to which lesion is actively bleeding. Adequate sedation is a prerequisite, al-

though barbiturates are to be avoided. Most endoscopists prefer gastric aspiration and saline lavage to clear the stomach and improve visualization. If esophageal varices are present and are not bleeding or have recently stopped bleeding, endoscopy is safe and is not likely to precipitate bleeding from varices.[8]

Arteriography

Selective arteriography has had increasing usefulness in the diagnosis (and treatment) of upper gastrointestinal bleeding. The decision to proceed with arteriography should be made early for maximum productivity, while active bleeding is occurring and before barium contrast studies, since residual barium may obscure or confuse the arteriographic findings. The venous phase outlines the patency and configuration of the portal circulation, demonstrates varices and may be used to estimate portal flow velocity. If diagnostic arteriography is performed, the catheter should be positioned and left in the superior mesenteric artery for possible later intra-arterial infusion.

Splenoportography

Splenoportography is a valuable and surprisingly safe procedure. Excellent visualization of the intrahepatic and extrahepatic configuration of the portal circulation is achieved and the presence of collateral channels (varices) can be demonstrated with good reliability. The splenic pulp pressure, measured percutaneously with a saline manometer, is generally an accurate indication of portal pressure when measured under local anesthesia. If strict adherence to technical precautions is observed, complications are infrequent and consist entirely of occasional persistent bleeding from the spleen requiring splenectomy or a small pneumothorax. If ascites is carefully controlled prior to the study, the platelet count is above 50,000 and the prothrombin time 15 seconds or less, these complications are uncommon (under 5 per cent).[6] If selective distal splenorenal shunt is anticipated, splenoportography is contraindicated, since damage to the spleen would preclude that procedure.

Splenoportography admittedly gives a clearer picture of portal circulation than venous phase arteriography, but in 5 to 10 per cent of patients, known varices are not demonstrated. Splenoportography does not provide the additional benefit of an arterial catheter for later infusion of vasopressors. In general, we have not found splenoportography as useful as arteriography in the diagnosis or management of massive upper gastrointestinal bleeding. It is more valuable in the elective evaluation of the patient who has stopped bleeding or in the patient with undiagnosed splenomegaly.

Barium Contrast Studies

The esophagogram and upper gastrointestinal series are a time-honored approach to the diagnosis of upper gastrointestinal disease and will certainly continue to be the heart of routine investigation. There are several inherent disadvantages, however: (1) In the actively bleeding patient with intragastric clot, adequate studies may be difficult. (2) Al-

Table 2. *Child's Classification*

	GROUP A	GROUP B	GROUP C
Serum bilirubin (mg per 100 ml)	Below 2.0	2.0–3.0	Over 3.0
Serum albumin (gm per 100 ml)	Over 3.5	3.0–3.5	Under 3.0
Ascites	None	Easily controlled	Poorly controlled
Neurologic disorder	None	Minimal	Advanced "coma"
Nutrition	Excellent	Good	Poor, "wasting"

though esophageal varices present a dramatic appearance when seen, they are frequently not demonstrated. (3) Acute gastritis and active peptic ulcer disease, in the actively bleeding patient, may be difficult to diagnose and the frequency of false negative results may be 40 to 50 per cent under these circumstances. In addition, when multiple abnormalities are present in the upper gastrointestinal tract, the barium contrast study fails to conclusively demonstrate which lesion is actively bleeding. Although some endoscopists prefer to have a barium study prior to endoscopy as a "road map," barium should be withheld if arteriography is anticipated.

Liver Function and Morphology

Marked derangement of liver function is an invariable accompaniment of portal hypertension when secondary to cirrhosis. BSP retention is a sensitive indicator of liver function and when normal virtually excludes cirrhosis as a cause of portal hypertension. It is a useful screening test in the emergency bleeder. An elevated BSP is suggestive of liver disease but is not diagnostic. Evidence of marked hepatic parenchymal dysfunction with hyperbilirubinemia, hypoalbuminemia, hypoprothrombinemia and general malnutrition, give further support to the diagnosis of underlying liver disease and together with physical examination, have been the basis for dividing patients into clinical categories as described by Child (Table 2). Percutaneous liver biopsy should be an integral part of the diagnostic evaluation if possible.

TREATMENT

The treatment of esophageal varices, at present, is founded on several well accepted axioms which have evolved over the past three decades. (1) Esophageal varices rarely, if ever, bleed unless the portal pressure is over 25 cm of saline. (2) At this time, the only successful, long-term treatment of bleeding esophageal varices is reduction of portal pressure (portal decompression) through creation of a major portasystemic (collateral) shunt. (3) When portal pressure is effectively reduced, bleeding from esophageal varices is very infrequent and when it occurs is usually evidence of shunt occlusion. (4) Portal decompression, though preventing recurrent bleeding, has otherwise adverse effects in a substantial number of patients, specifically, hepatic encephalopathy and accelerated liver failure. These side-effects are sufficiently

common to negate the value of prophylactic decompression in patients with varices that have never bled. This point has been clearly demonstrated in several well controlled collaborative studies which show long-term survival in operated and unoperated groups to be similar. (5) The mortality in patients undergoing emergency shunts approaches 50 per cent. This is 5 to 10 times the mortality of shunts constructed electively (following bleeding) so that elective surgery is preferable if adequate temporary nonoperative methods for control of bleeding are available.

Controversial areas in the management of bleeding varices center around several incompletely answered questions concerning patient selection, timing of operative intervention and technique of portal decompression.

Selection of Patients

Given the high incidence of hepatic encephalopathy and accelerated liver failure which often follows portal decompression, many investigators have attempted to define patient populations who may statistically be expected to tolerate operation and diversion of portal flow as opposed to populations who will have a prohibitively high operative and late mortality. Two categories of information have been evaluated with this end in mind. The clinical criteria, as represented by Child's classification, have proved to be an accurate predictor and clearly indicate that the more severe the underlying liver disease, the less likely is the patient to survive operation and portal diversion.[2] The elective operative mortality in the Class A and B patients is generally 10 per cent or less, whereas the mortality and long-term survival in Class C patients is prohibitive. On this basis, patients who fall into a Child's Class C category are generally not felt to be candidates for portacaval shunting.

Hemodynamic evaluation (portal vein and hepatic artery flow and perfusion pressures) have provided a large body of useful investigative data but have been disappointing as predictors of success or guides to choosing the type of shunt to be performed.[21] Liver biopsy to assess the degree of hyaline necrosis as described by Mikkelsen[13] has also proved to be an accurate predictor of survival, but depends upon the availability of a pathologist with experience in this field.

In general, patients who have or have developed marked liver failure and hepatic encephalopathy during a bleeding episode are not candidates for shunting. The best operative results and long-term survival follow decompression in Class A or Class B patients who have had a small, controlled hemorrhage.

Timing

Should emergency decompression be undertaken during the acute bleeding or should aggressive nonoperative or operative techniques be employed to stop bleeding and allow elective shunting at a later time?

Theoretically, operation during a non-bleeding period would result in the lowest overall mortality, but patient loss during nonoperative treatment may be high and controlled data supporting the superiority of one approach over the other is lacking at present. Operative techniques to directly control bleeding without shunting have been employed in

several centers. Transthoracic ligation of esophageal varices, as championed by Linton, can be a successful, albeit temporary, means of controlling massive hemorrhage. Unfortunately, the operative mortality from this nondefinitive procedure approaches the operative mortality from emergency shunting and the patient is still required to undergo a later decompression and a second operative risk.[18]

Esophagogastrectomy has been universally abandoned owing to the high mortality from anastomotic leaks and later re-bleeding. Esophagogastrectomy may have some benefit when employed in patients with extrahepatic portal block in whom a shunt procedure is not feasible or has failed. Splenectomy is to be avoided as a primary procedure, except in the rare instance in which varices have occurred from localized splenic vein thrombosis without portal vein obstruction or liver disease. In these instances, splenectomy is curative.

Nonoperative attempts to control bleeding varices and permit later elective decompression have gained an established place in treatment through the development of intra-arterial infusion of vasopressors. Commercially available extracts of posterior pituitary, e.g., vasopressin, when infused selectively into the superior mesenteric artery, cause local vasoconstriction with resultant decrease in arterial and portal flow and reduction in portal pressure. Early results are encouraging. Bleeding has been controlled in 40 of 41 patients by Nusbaum.[15]

If the nonoperative approach is unsuccessful, emergency decompression is indicated. Emergency operative intervention is still favored by Orloff.[16]

TECHNIQUES

A variety of imaginative techniques for portal systemic shunting have been described. Each has advantages and disadvantages and the ultimate choice rests on the individual circumstance and the experience of the surgeon. At present, there are four major types of shunts (Fig. 1).

Portacaval Shunts

Portacaval shunting may be accomplished by side-to-side anastomosis of the portal vein to the infrahepatic vena cava or by an end-to-side anastomosis of the distal portion of the divided portal vein to the vena cava. The theoretical advantage of a side-to-side shunt, i.e., permitting some continued portal perfusion of the liver, cannot be verified clinically: a side-to-side shunt usually totally diverts portal flow and no significant benefit can be attributed to either technique when employed for variceal bleeding.[17] If intractable ascites is present, the side-to-side shunt is superior. If the mean portal perfusion pressure is negative, indicating hepatofugal flow in the portal vein, it is unclear whether a side-to-side shunt offers lower morbidity than an end-to-side shunt. An end-to-side shunt is technically easier to construct and side-to-side shunts are not always feasible because of the presence of an enlarged quadrate lobe, the resection of which is not justified. Some authors have used an interposed graft between the portal vein and the vena cava.

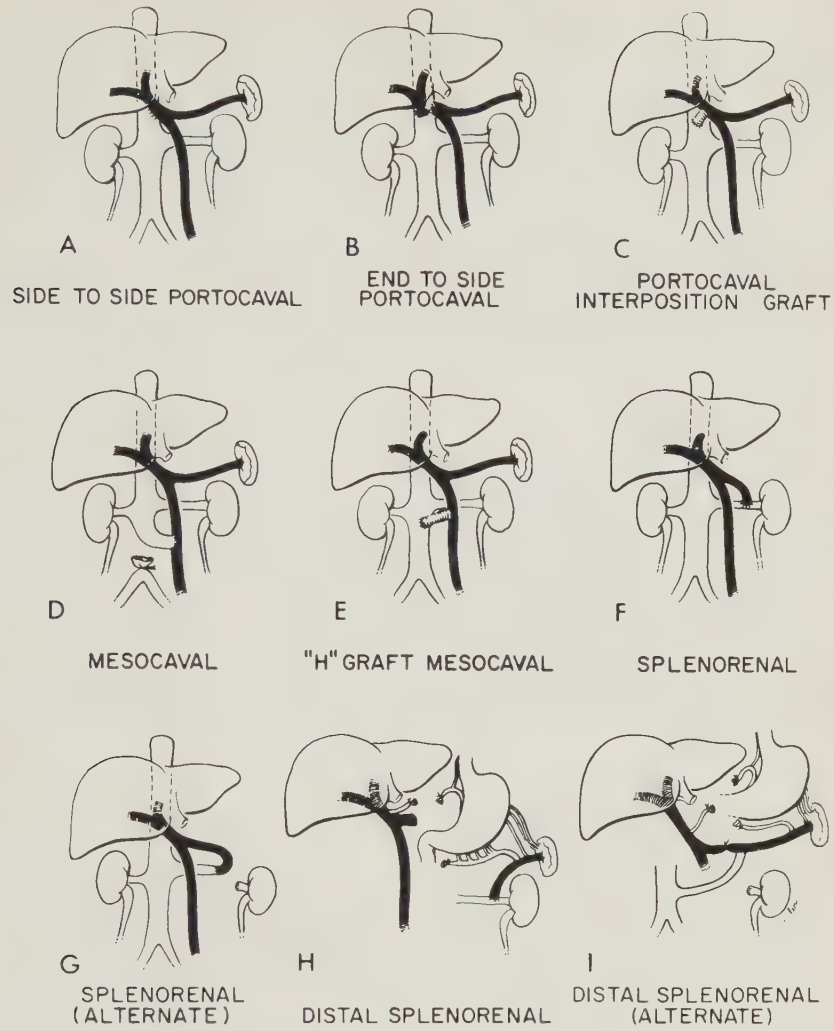

Figure 1. Varieties of portal decompression.

Mesocaval Shunt

A mesocaval shunt is indicated when primary or secondary thrombosis of the portal vein has occurred. The mesocaval shunt may be constructed by transecting the vena cava or right iliac vein, swinging the proximal portion up for end-to-side anastomosis to the mesenteric vein and ligating the distal vena cava or iliac vein. Troublesome edema of the lower extremities in the cirrhotic patient with hypoproteinemia has made this less than ideal and considerable clinical experience has been gained with the interposed "H" graft. Dacron arterial prosthesis, homologous vena cava, or autologous internal jugular vein may be used. The indications for the use of the "H" graft have been broadened by some to

include patients without portal vein thrombosis since the technique requires less dissection with less blood loss and shortened operating time. The early experience with the interposed "H" graft has generally been favorable. Thompson[22] reported excellent success using autologous internal jugular vein and Drapanas[4] has favored a Dacron prosthesis. The limited experience in Pittsburgh with Dacron prosthesis has been less favorable with 7 of 8 patients ultimately expiring. The superiority of the "H" graft over a standard portacaval shunt in elective decompression of the typical cirrhotic patient with a patent portal vein has yet to be adequately documented in a controlled study. "H" grafts clearly function as complete diversion and the long-term success when employed in primary portal thrombosis without liver disease is excellent. They have adequately controlled ascites when this has been an intractable problem.

Splenorenal Shunt

The splenorenal shunt in which the proximal splenic vein is brought end-to-side to the left renal vein or alternately the transected left renal vein to the splenic vein has been advocated as a method of achieving good portal decompression for control of variceal bleeding but with a lesser incidence of hepatic encephalopathy. This technique has proved useful where portal vein thrombosis is present but is technically exacting and may be associated with a higher frequency of thrombosis. It has failed to gain a wide-spread acceptance in preference to a portacaval shunt. If a previous splenectomy has been performed, the splenic vein is unusable.

Selective Shunting

Because of the distressing incidence of hepatic encephalopathy and accelerated liver failure when complete portal diversion is achieved, interest in techniques to selectively decompress the esophageal variceal bed without disrupting portal flow has grown. The coronocaval shunt as described by Linton has been successfully employed. More recently, the distal splenorenal shunt as developed by Warren and Britton appears to be a theoretically sound approach. The distal end of the divided splenic vein (with the spleen undisturbed) is anastomosed to the left renal vein with ligation of the coronary and gastroepiploic vein. Alternately, the proximal end of the divided left renal vein may be brought up to the splenic vein with ligature of the splenic vein proximal to the anastomosis. Sufficient long-term experience with this technique is, as yet, unavailable to recommend its wide adoption, but Warren[24] reports a low incidence of encephalopathy. Lunderquist[9] has recently described selective sclerosis of the coronary vein by a percutaneous transvenous route in 4 patients. The long-term value of this approach has yet to be evaluated.

Our Approach to the Bleeding Patient

In general, we have favored an aggressive attempt to control bleeding nonoperatively and follow this with a period of careful medical management and later portal decompression during the same hospital admission.

During the acute upper gastrointestinal bleeding, the stomach is aspirated and iced saline lavage is begun through a large bore tube. Esophagogastroscopy is employed early and if variceal bleeding is identified, a Sengstaken-Blakemore tube is inserted. Applying this external compression to the variceal bed is frequently successful in short-term control of bleeding. It may serve as a diagnostic test in the acutely hemorrhaging patient. The technique and results of the use of the Sengstaken-Blakemore tube have been reviewed by Bauer.[1] Several precautions are necessary to prevent an excessive complication rate. A nasogastric tube inserted through the opposite nostril to drain the esophagus above the esophageal balloon is necessary to prevent aspiration. Care must be taken to prevent inadvertent retraction of the esophageal balloon and obstruction of the nasopharynx. Both these complications can be eliminated if an endotracheal tube is used concomitantly and this is favored by many authors. The esophageal balloon must be deflated at 24 to 48 hours to prevent ischemic pressure necrosis with mucosal ulceration and occasional esophageal rupture.

If the diagnosis remains in doubt or if the Sengstaken-Blakemore tube is unsuccessful, arteriography is undertaken for diagnosis and treatment. If no arterial bleeding site is identified, venous phase angiography is completed to outline the portal bed and demonstrate collateral channels, although actual bleeding from varices can rarely be demonstrated. The catheter is positioned and secured in the superior mesenteric artery beyond any anomalous hepatic arterial branches for direct intra-arterial infusion of vasopressin (Pitressin). If bleeding has continued, infusion of vasopressin at the rate of 0.1 to 0.3 units per minute into the superior mesenteric artery is begun for a period of up to 24 hours and intermittently thereafter. It is important to begin vasopressin early before multiple transfusions deplete clotting factors and make success less likely. There are few complications, other than those of arterial catheterization in general. If posterior pituitary extract is used, one must compensate for the antidiuretic effect. The technique, results, and complications have been reviewed by Nusbaum and Baum.[15]

The clinical use of mesenteric artery vasopressin infusion has been recently expanded. In the cirrhotic with known esophageal varices who is bleeding from a nonvariceal site, the mortality from emergency operative intervention has been so high[25] that vasopressor treatment for this group of patients has been tried with marked success and increased survival.[19] In addition, vasopressor infusion has been used during elective shunting procedures to substantially reduce the amount of blood loss during the dissection necessary for creating a major shunt.[14]

If these nonoperative methods are unsuccessful, we have preferred progressing directly to portal decompression and have not favored transthoracic esophageal variceal ligation. Patency of the portal vein should be determined preoperatively and careful pressure measurements should be recorded at laparotomy. We have utilized a generous right upper quadrant incision. The portal vein is temporarily occluded with a vascular clamp and pressures are measured on either side. If the pressure distally is greater than that between the clamp and the liver, this is designated a positive perfusion pressure, indicating normal direc-

tion of portal blood flow. If the mean portal perfusion pressure is positive, an end-to-side portacaval shunt has generally been employed, whereas if the portal perfusion pressure is negative (evidence of hepatofugal portal blood flow), then side-to-side portacaval shunt or an interposed graft is suggested. Following completion of a major shunt, pressures should be re-measured and a drop of at least 10 cm of saline is to be expected, although an immediate drop to systemic venous pressure is infrequent.

The frequency of hepatic encephalopathy may be reduced by lowering the bacterial count in the large bowel and carefully cleansing the intestinal tract of shed blood both preoperatively and postoperatively. Neomycin sulfate may be administered per os in a dose of 4.0 to 6.0 gm per day in divided doses for 48 hours and 1.0 to 3.0 gm daily thereafter. Oral protein intake should be limited. Neomycin sulfate may be administered in a retention saline enema. Diuretics should be used as necessary with careful monitoring of serum electrolytes. Caloric intake may be maintained by use of hypertonic glucose through tube feeding or intravenously. In general, we have been reluctant to operate on Child's Class C patients.

CONCLUSION

Despite the apparent conflict and confusion, an increasingly standardized approach to portal hypertension appears to be emerging. Portal decompression of the patient with benign extrahepatic portal obstruction by means of mesocaval shunt is highly successful with few complications.[7] In the cirrhotic population which comprises the bulk of patients with variceal bleeding, only portal decompression, at the present time, offers long-term relief from recurrent hemorrhage in patients who have bled. Those who have never bled should not undergo prophylactic decompression and patients with intractable ascites or hypersplenism secondary to portal hypertension rarely require decompression. In the patients with acute massive upper gastrointestinal bleeding, improved nonoperative techniques, in particular, intra-arterial perfusion of vasopressin, allows many patients to be decompressed later, when not bleeding, with greatly reduced mortality. At present, there is little objective data to favor any particular type of central shunt—all are effective and have roughly the same operative mortality and associated incidence of hepatic encephalopathy.

The primary goal, at present, is to find ways of avoiding hepatic encephalopathy and the adverse effects of deprivation of portal flow on the liver, either through selective decompression of the variceal bed or portal arterialization. Radical new approaches, such as liver transplantation, when that becomes feasible, may be the ultimate answer. With the incidence of cirrhosis rising, this subject remains a fertile field for investigation and innovation.

REFERENCES

1. Bauer, J. J., Kreel, I., and Kark, A. E.: The use of the Sengstaken-Blakemore tube for immediate control of bleeding esophageal varices. Ann. Surg., *179*:273–277, 1974.
2. Campbell, D. P., Parker, D. E., and Anagnostopoulos, C. E.: Survival prediction in portacaval shunts: A computerized statistical analysis. Amer. J. Surg., *126*:748–751, 1973.
3. Child, C. G., III: Portal Hypertension As Seen by Seventeen Authorities. Philadelphia, W. B. Saunders Co., 1974.
4. Drapanas, T.: Interposition mesocaval shunt for treatment of portal hypertension. Ann. Surg., *176*:435–448, 1972.
5. Forrest, J. A. H., Finlayson, N. D. C., and Shearman, D. J. C.: Endoscopy in gastrointestinal bleeding. Lancet, 2:394–397, 1974.
6. Foster, J. H., Conkle, D. M., Crane, J. M., et al.: Splenoportography: An assessment of its value and risk. Ann. Surg., *179*:773–781, 1974.
7. Lambert, M. J., III, Tank, E. S., and Turcotte, J. G.: Late sequelae of mesocaval shunts in children. Amer. J. Surg., *127*:19–24, 1974.
8. Lopez-Torres, A., and Waye, J. D.: Safety of intubation in patients with esophageal varices. Amer. J. Dig. Dis., *18*:1032–1034, 1973.
9. Lunderquist, A., and Vang, J.: Transhepatic catheterization and obliteration of the coronary vein in patients with portal hypertension and esophageal varices. New Eng. J. Med., *291*:646–649, 1974.
10. Marks, C.: The Portal Venous System. Springfield, Illinois, Charles C Thomas, 1973.
11. McDermott, W. V., Jr.: Surgery of the Liver and Portal Circulation. Philadelphia, Lea and Febiger, 1974.
12. Mendenhall, C. L., Sherman, J., and Chedid, A.: Intermittent idiopathic portal hypertension. A case report. Gastroenterology, 67:142–148, 1974.
13. Mikkelsen, W. P.: Therapeutic portacaval shunt. Preliminary data on controlled trial and morbid effects of acute hyaline necrosis. Arch. Surg., *108*:302–305, 1974.
14. Nusbaum, M., Younis, M. T., Baum, S., et al.: Selective superior mesenteric arterial infusion of vasopressin during portosystemic shunt operations. Amer. J. Surg., *127*:35–39, 1974.
15. Nusbaum, M., Younis, M. T., Baum, S., et al.: Control of portal hypertension—Selective mesenteric arterial infusion of vasopressin. Arch. Surg., *108*:342–347, 1974.
16. Orloff, M. J., Chandler, J. G., Charters, A. C., III, et al.: Emergency portacaval shunt treatment for bleeding esophageal varices. Arch. Surg., *108*:293–299, 1974.
17. Orloff, M. J., Chandler, J. G., Charters, A. C., III, et al.: Comparison of end to side and side to side portacaval shunts in dogs and human subjects with cirrhosis and portal hypertension. Amer. J. Surg., *128*:195–201, 1974.
18. Ottinger, L. W., and Moncure, A. C.: Transthoracic ligation of bleeding esophageal varices in patients with intrahepatic portal obstruction. Ann. Surg., *179*:35–38, 1974.
19. Ring, E. J., Baum, S., Athanasoulis, C., et al.: Angiography in the diagnosis and treatment of non-variceal bleeding in patients with portal hypertension. Surg. Gynec. Obstet., *139*:205–207, 1974.
20. Sherlock, S.: Classification and functional aspects of portal hypertension. Amer. J. Surg., *127*:121–128, 1974.
21. Smith, G. W.: Use of hemodynamic selection criteria in the management of cirrhotic patients with portal hypertension. Ann. Surg., *179*:782–790, 1974.
22. Thompson, B. W., and Read, R. C.: Interposition "H" grafting for portal hypertension. Arch. Surg., *108*:502–506, 1974.
23. Vos, L. J. M., Potocky, V., Broker, F. H. L., et al.: Splenic vein thrombosis with esophageal varices. Ann. Surg., *180*:152–156, 1974.
24. Warren, W. D., Salam, A. A., and Smith, R. B., III: The mesospleno-renal shunt procedures: A comprehensive approach to portasystemic decompression. Ann. Surg., *179*:791–798, 1974.
25. Wirthlin, L. S., Urk, H. Van, Malt, R. B., et al.: Predictors of surgical mortality in patients with cirrhosis and non-variceal gastroduodenal bleeding. Surg. Gynec. Obstet., *139*:65–68, 1974.

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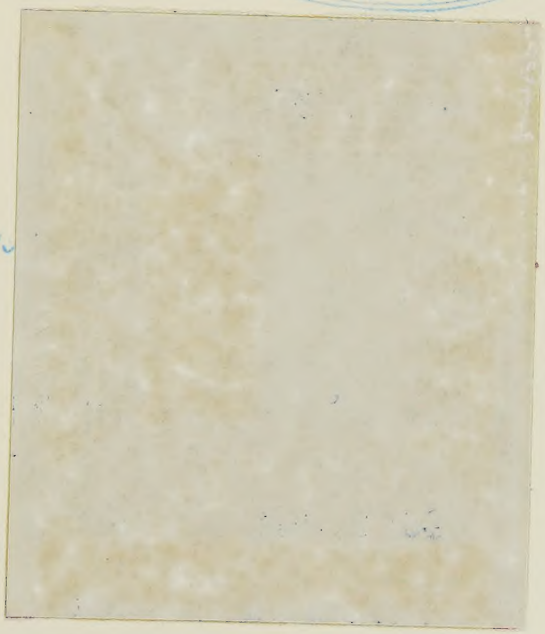

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